University of Alberta

Early Life Determinants of Asthma and Wheezing: A Longitudinal Study of Canadian Children

by

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Dedication

This dissertation is dedicated to my dear children: Sena, Emefa, and Ely; and my loving wife, Christine for their support, patience, and encouragement accorded me to attain this educational goal.

Also, to my mother, Jane, my father, Emmanuel, and my aunt, Agnes for the inspiration you have provided to me since the early stage of my journey toward this educational pinnacle.

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Abstract

Asthma is a major public health problem associated with significant health care costs worldwide. The "hygiene hypothesis" advocates early exposure to infections and other environmental factors may prevent the development of asthma. This thesis used the Canadian National Longitudinal Survey of Children and Youth (NLSCY) to examine: 1) the influence of dwelling in a farming environment on the development of asthma; 2) the impact of perinatal and early-life exposures on the development of asthma and wheeze; and 3) the risk factors for wheezing phenotypes in the first decade of life. Prospective data on child, parental, and household factors were collected every two years between 1994 and 2003 at five time points in the NLSCY. For the first objective, longitudinal data from the first two cycles were used and baseline risk factors for the development of asthma at the second cycle were determined. For the second objective, longitudinal data from infant and toddler cohorts from Cycle 2 and Cycle 4 and Cycle 3 to Cycle 5 were used to determine the risk factors for the incidence of asthma and wheezing. For the third objective, wheezing patterns in the first decade of life were used to determine the risk factors for four different phenotypes. Advanced statistical methods including bootstrap and modified stepwise techniques were used to adjust for complex survey sampling. After a 2-year follow-up, dwelling in a farming environment was found to be protective for the development of asthma (odds ratio (OR) 0.47; 95% confidence interval (95% CI), [0.35-0.64]) in children (less than 12 years of age) and this association was modified by parental history of asthma. Among preschoolers (<6 years), predictors of lower incidence of asthma were infant wheezing, breast feeding for more than three months, nose and throat infections in early-life, early daycare attendance, having two or more siblings and dwelling in non-urban areas. Daycare attendance in the first year of life was a risk factor for wheezing during preschool but was protective for wheezing during primary school. In conclusion, this large population-based study confirms that early childhood environmental exposures are important etiological factors for the development of asthma and wheezing.

Preface

This thesis was conducted to determine early life factors associated with development of asthma and wheezing in childhood. The main parts of the study are presented in Chapters 2 to 4. First, an overview is presented of the epidemiological risk factors for childhood asthma and wheezing in Chapter 1. Next, Chapter 2 presents a study that was conducted among children of ages less than 12 years to assess whether or not dwelling in a faming environment was associated with the onset of asthma. In the analysis, longitudinal data from the first two cycles of the NLSCY was used to determine the impact of the baseline dwelling environment and development of asthma at the second cycle. Chapter 3 presents the results of a study conducted among preschoolers (<6 years) to examine whether or not environmental exposures that increase the likelihood for early infection in infants and toddlers reduce the risk of developing asthma and wheezing among preschoolers (2 to 5 year olds). Finally, Chapter 4 presents the findings from a study that examined the early-life risk factors for predicting wheezing phenotypes in the first decade of life when children (less than 2 years) were indexed at baseline and followed-up for 5 waves until they were 9 to 10 years of age. Each chapter includes its own introduction, methods, results, discussion, and set of references. Chapter 5 provides an overall summary of results, discussion, and conclusions.

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Disclaimer: "The research and analysis are based on the data from Statistics Canada and opinions expressed herein do not represent the views of Statistics Canada."

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List of Symbols and Abbreviations

AIC	Akaike Information Criteria
ANOVA	ANalysis Of VAriance
BHR	Bronchial HyperResponsiveness
BMI	Body Mass Index
CCHSA	Canadian Center for Health and Safety in Agriculture
CI	Confidence Interval
CIHR	Canadian Institute of Health Research
CMA	Central Metropolitan Areas
ECD	Early Childhood Development
ED	Emergency Department
ETS	Environmental Tobacco Smoke
FEV_1	Forced Expiratory Volume in 1 second
FVC	Force Vital Capacity
GINA	Global Initiative on Asthma
HR	Hazard Ratio
HRDC	Human Resource Development of Canada
IgE	Immunoglobin E
ISAAC	International Study of Asthma and Allergies in Children
LBW	Low Birth Weight
LFS	Labor Force Survey
NHLBI	National Heart, Lungs and Blood Institute
NLSCY	National Longitudinal Survey of Children and Youth
NPHS	National Population Health Survey
OR	Odds Ratios
PEF	Peak Expiratory Flow
PHARE	Public Health and Agricultural Rural Ecosystem
PMK	Person Most Knowledgeable
RDC	Research Data Centre
SES	Socio-Economic Status
SIC	Schwarz Information Criteria
SUDAAN	SUrvey DAta ANalysis
Th1	T helper type 1 cells
Th2	T helper type 2 cells
VRTI	Viral Respiratory Tract Infection
WHO	World Health Organization

Chapter 1

Introduction

1.1 Background

Asthma is a chronic inflammatory disorder of the airways in the lungs that can affect both children and adults. It is characterized by shortness of breath or dyspnea, cough, and chest tightness that are reversible with medication, and at times, removal of airway irritant.[1] The exact reason for the onset of asthma is still not clear, although the interaction between factors related to an individual's genetic make-up and environmental conditions are believed to play a major role in its development.[2-6] Patients with active asthma usually wake up at night or early in the morning with one or more symptoms of wheezing, chest tightness, shortness of breath and cough; and also experience acute exacerbation to non-specific stimuli such as upper respiratory infection (URI), cold air, or respiratory irritants. Even though the diagnosis for asthma among young children may not be definitive until the age of five years, an early symptom of wheezing among infants or toddlers may be indicative of those who are at increased risk for developing the disorder later in life.[1] About 25% of preschool children who are later diagnosed with asthma in their school years, have had some symptoms of wheezing in their first year of life, and over 80% of adults with active asthma have had some related symptoms when they were younger than 6 years old.[7,8]

1.1.1 Burden of Asthma Illness

1.1.1.1 Worldwide

Asthma is a major public health problem associated with significant health care cost worldwide.[9-11] The disorder constitutes a significant proportion of both acute and chronic illness among children and is responsible for considerable pediatric emergency visits, hospitalizations, school absenteeism, and reduced participation in active family life.[9,12] Strong evidence suggests that the prevalence, morbidity, mortality, and economic burden of asthma has increased worldwide, particularly among children since the early 1960s,[9,13-15] but limited knowledge is available to explain this increase. In particular, a greater burden of asthma has been observed in developed countries than in developing countries.[9,13] In a recent review, the highest prevalence of asthma was found in the United Kingdom or UK (>15%), New Zealand (15.1%), Australia (14.7%) the Republic of Ireland (14.6%), Canada (14.1%) and the USA (10.9%).[9,13] According to a recent report from the World Health Organization (WHO), 300 million children and adults lived with active asthma worldwide in 2005, and the estimated death toll from asthma alone was 255,000,[11] although overall mortality rates have fallen since the 1980s. In North America, 1 in 10 persons (equivalent to approximately 35.5 million individuals) have asthma.[13] In the USA alone, an estimated 20.3 million individuals have asthma. Of these, 12 million (4 million under the age of 18 years) reported attacks in 2001 (American Lung Association, Key facts about Asthma). By 2020, asthma is expected to strike 1 in 14 individuals, or 1 in 5 families dwelling in the USA.[16] Between 1993 to 1995, deaths have doubled to over 5,000 in the USA, [17] and the increasing trend in morbidity was evident among all age groups, sexes, and race strata, with the most substantial increase seen among children under the age of 15 years.[12,17]

Over the last decade, however, evidence from studies conducted in some developed countries, including the USA,[18] Canada,[19] and the UK[20] suggests that a stabilizing or decreasing trend is occurring in asthma morbidity and hospitalization rates. The average estimate of financial burden reported for asthma in different Western countries ranges from $300 to $1,300 (USD) per patient per year.[9] In 2002, the direct and indirect economic burden of all forms of asthma in the USA came to a total of $14 billion, including $9.4 billion in direct costs, and $ 4.6 billion in indirect costs (missed school and work days).[21] The 2000 WHO report indicated that the economic costs associated with asthma alone worldwide exceed those of tuberculosis and HIV/AIDS combined.[10]

1.1.1.2 Burden of Asthma in Canada

Asthma is a leading cause of hospitalization, emergency department (ED) visits, and missed school days among children in Canada. It accounts for approximately 80% of all chronic respiratory disease, affecting about 8.4% of the population living in Canada.[22] The prevalence and hospital admissions have significantly increased over the past three decades, and today, asthma exerts a huge cost on the Canadian health care system.[23,24] According to a Canadian National Population Health Survey (NPHS), an estimated 2.4 million Canadians suffer from asthma (NPHS, 1998-1999); the prevalence among children is as high as 12% (NPHS, 1996-1997). Every year, more than 146,000 emergency room visits are due to asthma in Canada. In 1994 alone, asthma accounted for approximately 54,532 admissions to Canadian hospitals.[23] More than 500 Canadian children and adults die each year from asthma attack.[25]

The economic cost of asthma in Canada is staggering. In a recent study, the all-cause outpatient claim cost for individuals with asthma in Ontario far exceeded those without the condition.[26] From a compilation of statistical information in Canada, in 1993 alone, over $12 billion was spent on asthma,[23,27] and the cost of hospitalizations in 1994 was $135 million.[28] The direct and urgent care cost associated with resources used by individuals with asthma in Canada, which include hospitalizations, unscheduled physician visits, emergency department visits, drug treatments, nursing and ambulance services, is estimated to be from $162 million to $600 million per year.[24,25,29] Indirect losses include missed school days and lost parental work hours due to care. Despite a better understanding of the effects of therapy and the cause and improvements of this disease, asthma continues to inflict a significant burden on human and health care cost in Canada.

1.2 Rationale for this Doctoral Research

To the best of my knowledge, no longitudinal, large-scale, population-based epidemiologic study has yet been conducted nationwide in Canada to investigate the risk factors for the progression of asthma among children, although some authors have offered opinions on the issue.[19,30,31] Large-scale, cohort studies conducted across wide geographic areas, especially using standard questionnaires to measure outcomes of asthma and related symptoms, are needed to understand the geographic differences and factors associated with the development of asthma early in life. In summary, this thesis used data from the Canadian National Longitudinal Survey of Children and Youth (NLSCY), conducted between 1994 and 2003 to explore early-life factors such as prenatal, perinatal, familial, household, and environmental factors associated with the development of asthma and wheezing among children in Canada.

1.3 The Canadian NLSCY

A long-term population study of children, the NLSCY, was initiated in Canada to monitor the impact of factors affecting the development and well-being of children followed from birth to early adulthood. The study began in 1994 across all 10 provinces and three territories in Canada under the federal government's "brighter initiatives" for children dwelling in Canada. The three main objectives of the NLSCY were to:

1) determine the prevalence of various risk and protective factors for children and youth;

2) understand how these factors, as well as life events, influence children's development;

3) make this information available for developing policies and programs that will help children and youth.

Details of the survey components have been presented elsewhere,[32] and brief overview and sample distributions are presented in Appendix A of this thesis. The design of the NLSCY study used multistage sampling to collect information on individual child, parent, and household factors. Information on prenatal, perinatal, early childhood, socio-demographic, parental, emotional, and behavioural factors, that may influence the development of health outcomes among children over time, was collected. The survey also covers a comprehensive range of development of health outcomes as well as learning preparedness of children at a school age. Currently, research information is being generated from the NLSCY data by a variety of investigators at all levels of government, and in universities and policy-making organizations.[33]

To conduct this thesis, Statistics Canada granted permission to use the data from NLSCY surveys conducted from 1994 to 2003. This included five longitudinal panels introduced at five different cycles conducted two years apart (see Figure 1.1): Cycle 1 (1994-1995), Cycle 2 (1996-1997), Cycle 3 (1998-1999), Cycle 4 (2000-2001), and Cycle 5 (2002-2003). Only Panel 1 (children, less than 12 years of age, introduced at Cycle 1 or baseline) has data for all five waves. The intent of the NLSCY study was to follow the Panel 1 children until they attained the age of 25 years. Panel 2 was the first "Early Childhood Development (ECD)" cohort of children age less than 2 year old, introduced at Cycle 2. This panel and the three subsequent panels of ECD cohorts introduced at Cycle 3, 4, and 5 were to be followed until the children attained the age of 5 years (Figure 1.1). The objective of the ECD study was to monitor the early development of children before they attend school (< 6 years). See Appendix A for detail information related to the data used in this thesis. NLSCY data from the three territories were stored separately from the data for the 10 provinces and were not included in the thesis.

1.4 Foundations for the Research Problem

Observations made over the last three decades indicate that improved lifestyle, urbanization, and increased use of antibiotics for treatment and hygiene in most developed countries has paralleled the dramatic increase in occurrence of allergies and asthma in these countries. This led to the proposal of the "hygiene hypothesis" that:[34]

> the decrease in the factors that may increase the likelihood of exposure to bacterial and parasitic infection from the natural or traditional environments in these developed countries may be responsible for the increased morbidity of atopic diseases including asthma.

Generally, newborn infants are known to have T-helper 2 (Th2) skewed immune responses. Th2 cells enhance the allergic activity by increasing the production of allergic antibody Immunoglobin E (IgE) cells. In contrast, T-helper 1 (Th1) immune cells help to defend against intracellular infections. Recent knowledge indicates that, when factors which increase the immune-maturing of defences against infections are absent in young infants and toddlers, they remain prone to the development of a Th2 response and thus, continue to experience symptoms of atopic disease including asthma later in childhood.[2,3,35,36] Therefore, the basic principle of the hygiene hypothesis advocates that an opportunity for early infection is important to balance the Th1 and Th2 cell ratio for the proper regulation of a balanced immune response in neonates and infants.

In the last decade, several epidemiological studies conducted around the world have found strong support for this hypothesis based on the observation that traditional lifestyles and environments associated with increased infections, such as dwelling in a farming environment,[37-53] daycare attendance,[31,54-56] and large sibships or family size[8,31,54,57] are associated with a lower prevalences of atopic diseases including asthma. A recent report indicates that, in developing regions particularly Africa, Central and South America, Asia, and the Pacific, prevalence of asthma continues to rise sharply, in parallel with the increasing shift of individuals from rural dwellings to urbanization and Westernization.[9] Since most of these findings were obtained from cross-sectional studies, however, these variables may be mere associative factors with no significant or important etiological consequences in the onset or persistence of asthma.

Several studies have also indicated that, the development of asthma and wheezing in children share some common risk factors, including exposure to environmental tobacco smoke, difficult living conditions (low socio-economic status (SES), crowding), and male sex. The identification of an independent effect of wheezing in early life on subsequent development of asthma later in life may help to identify infants and toddlers who are at risk, so that early intervention programs may be initiated.

Finally, different phenotypes with varying expression of wheezing patterns have been observed among young children as they transit to adolescence and young adulthood.[58-60] There is evidence to suggest that the development of wheezing illness among infants and young children may not be a single disease or a homogeneous entity. For example, Martinez *et al.* reported that "transient wheezers" may stop wheezing by the age of three years, while "persistent wheezers" would continue to wheeze from the first year of life until the school-age.[60] At present, only a few studies have been conducted to understand the early life factors associated with these wheezing phenotypes that occur predominantly among young children.[61-63] Longitudinal investigations may help to elucidate the different expressions of this complex disorder and identify early life risk factors associated with phenotypes. The findings from such studies may facilitate public health intervention to reduce the burden of asthma among Canadian children.

1.4.1 Research Hypothesis

The main hypothesis of my research is: "prenatal, perinatal, and early life-related factors will be predictive of early occurrence of asthma and wheezing incidence among children."

1.4.2 Research Objectives

In this thesis, the main objectives are to:

1) test if dwelling in a farm environment protects against developing asthma among children aged less than 12 years;

2) determine if factors which increase the likelihood of exposure to infections, such as early daycare attendance and number of siblings at birth, reduce the incidence of asthma;

3) determine if early wheezing at infants and toddlers age (<2 years of age) increases the risk of developing asthma at the preschool age (2-5 years);

4) assess if development of asthma and wheezing at a preschool age (2-5 years) have the same prenatal, perinatal, and early-life risk factors; and

5) examine if different wheezing phenotypes that occur in the first decade of life have the same risk factors.

1.5 What is Asthma?

1.5.1 Clinical Definition

Both clinicians and medical researchers over the last three decades have faced considerable challenges in providing a consensus definition for asthma.[1] This has been mainly due to the many phenotypic expressions or progressions of asthma among children as they progress through adolescence to young adult life. Also, the clinical expression of asthma – characterized by wheezing, chest tightness, shortness of breath and coughing – are non-specific, and are common to other forms of airway diseases. The heterogeneity in the clinical manifestation of asthma in both paediatric and adult patients has posed challenges to even experienced experts in deriving a consensus definition.[1]

Variable airflow obstruction, with the presence of reversible airway obstruction to treatment have been highlighted in both past and present attempts to define asthma.[1,64,65] The recent international consensus[1,2,66] defined asthma as a:

chronic inflammatory disorder of the airway in which many cells and cellular elements play a role, in particular mast cells, eosinophil, T lymphocytes, macrophage, neutrophil, and epithelial cells. In susceptible individuals, these cells and their resultant activity cause inflammation and result in recurrent or persistent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes usually occur with widespread but variable airflow obstruction that often resolves itself either spontaneously or with treatment. The inflammation may also causes an associated increase in the existing bronchial hyper-responsiveness to a variety of stimuli.[1,2,66]

1.5.2 Pathogenesis

The exact cause leading to the onset of asthma is widely debated.[1] Nevertheless, a combination of genetic predisposition and exposure to environmental allergens and irritants are believed to play a major role in its development among individuals.[1-3,5,36] Over 90% of children with asthma are known to have a strong allergic component, with an inflammation response that is characterized by swelling of the lining of the airways.[1,64] Increased mucus hyper-secretion and bronchial hyper-reactivity, and bronchial airways narrowing that causes shortness of breath, wheezing, and cough, are the main symptoms observed in an asthma episode.[1]

Mast cells are known to be important in the development and exacerbation of asthma, though macrophage, neutrophil, and eosinophil cells also play a major role in aggravating the condition. Figure 1.2 presents an overview of the two steps that may be involved in the allergic pathophysiology or etiology of the disorder. When the airway of an allergic individual is sensitized with an allergen (e.g., pollen from ragweed, house dust mite, etc.), an allergic antibody, specifically immunoglobin E (IgE), attaches itself to the mast cell in the lining of the bronchial airways. Upon later re-exposure to the allergen, IgE binds to the allergen and causes the mast cell to degranulate. The degranulation releases histamine and arachidonic acid metabolites, such as leukotriene and prostaglandin. The action of these chemicals initiates early contraction of the smooth muscle in the airways. In addition, the chemicals cause leakage of fluid into the lungs, irritation of cough nerves, and swelling of the bronchial tubes, which marks the early phase of asthma with mild symptoms of coughing, wheezing, and shortness of breathe (Figure 1.2).

The late phase reaction usually occurs within a few hours when an influx of other cells especially eosinophils occurs in the lung.[1] The cells are attracted to the lung by the chemical mediators released by the mast cell degranulation in the early phase. The late phase response is clinically characterized by more profound coughing, wheezing, and shortness of breath due to increased bronchial hyper-responsiveness. The late phase response enhances the sensitization to non-allergic stimuli such as irritants and weather conditions that make asthma worse.[1]

1.5.3 Diagnosis

Usually, the clinical diagnosis for asthma is made by objectively demonstrating reversible obstruction of the airways. Individuals with asthma may have reduced lung function values in comparison to those of healthy subjects of similar sex, age, and height, which are determined using normal equations.[67,68] As part of the lung function tests, forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), FEV_1 /FVC ratio and Forced midexpiratory flow rate (FEF_{25-75}) are measured and compared to those of normal individuals. An increase in FEV_1 (usually >12% to 15%) in response to a bronchodilator is also used for a diagnosis of asthma.[2,69,70] Broncho-provocation or the provocative concentration at which patients will have a 20% fall in FEV_1 from baseline (PC_{20}) to methacholine or histamine challenge is used to assess the degree of bronchial hyper-responsiveness in asthmatic patients (Figure 1.3). Exercise challenge tests are also performed in children to diagnose asthma.[71,72] Most exercise physiologists consider a decrease of more than 10% in peak expiratory flow rate (PEFR) to be consistent with asthma, and a decrease of greater than 15% in PEFR, to be consistent with induced bronchospasm.[73] For therapeutic purposes, a diagnosis of asthma is usually presented in four categories as: intermittent, mild persistent, moderate persistent, and severe persistent asthma, based on severity of symptoms present.[2,69,70]

The diagnosis of asthma among children, especially infants and toddlers who are less than three years old, is limited by inherent difficulties in obtaining objective measures of lung function and airway inflammation. Also, some of the symptoms of asthma (e.g., wheeze, breathlessness, chest tightness, and sputum) are common to other lung diseases and can be misdiagnosed as bronchitis and/or respiratory tract illness due to virus or other infections, making treatment with antibiotics or cough suppressants ineffective. In some cases, diagnoses of asthma can be overlooked in children who present chronic symptoms such as cough, but without the classical symptoms of wheezing. Nevertheless, the risk of early childhood asthma can be ascertained after ruling out all non-asthmatic wheezing illnesses.[2,69,70] Chest radiographs are usually necessary to rule out other causes of wheezing or coexisting diseases in this age group, including cystic fibrosis, anatomic abnormalities, foreign body aspiration, gastrooesophageal reflux or vocal cord dysfunction before ascertaining the diagnosis of asthma.

1.5.4 Treatment, Management, and Control of Asthma

The Global Initiative on Asthma (GINA) and the National Heart, Lungs and Blood Institute (NHLBI) guidelines outline the diagnosis and management of asthma for both children and adults.[64,74] A recent update for the diagnosis and a stepwise management of asthma among children has been published.[75,76] Generally, the present treatment and management of asthma involves one of the following two approaches, based on the severity of the disease: 1) short-term or quick relief therapy; and 2) long-term preventive therapy. For short-term relief of asthma, the most potent and rapidly acting therapy is administration of the short-acting (e.g., albuterol, terbutaline) and long-acting (e.g., salmeterol, formoterol) β_2-adrenergic drugs, also referred to as bronchodilators.[1,2,70] They are available in multiple forms (short-, immediate-, and long-acting) and delivery systems (meter-dose inhalers, nebuliser solution, oral liquid or tablet, and respirable powder). Other medications for therapy include anticholinergic agents, theophylline, cromolyn, nedocromil; luekotriene antagonists; and glucocorticoids.[1] Long-term management of asthma symptoms is aimed at controlling the inflammatory process involved in the disease. This involves the use of anti-inflammatory medications such as corticosteroids.

To date, only a few asthma medications have been approved for use in childhood populations, although the benefits of continuous, long-term use of anti-inflammatory medications on asthma control are now clear from results of the long-term-clinical trial conducted among children.[77]

1.6 Defining Asthma in Epidemiological Studies

Defining asthma for epidemiological studies has also been a challenge for researchers[78,79] To date, various definitions have been used in the body of current literature to measure asthma, with no unified consensus among researchers. With the lack of a standardized definition, comparisons of prevalence reports from different parts of the world have been problematic. Nevertheless, a standardized questionnaire was implemented in the ongoing international study of asthma and allergies in childhood (ISAAC).[80] In addition to using the symptoms questionnaire, lung function tests, bronchial provocations tests, and exercise tests have been used in some epidemiological studies.[81]

1.6.1 Questionnaire Measurements

The most frequent measures employed for asthma in population studies are symptom questionnaires.[81] Usually, parents are used as proxy respondents to obtain information, especially among children who are less than five years old. Variant forms of the operational questionnaire have been used in the literature to measure asthma symptoms. Some of these include:

1) "***life time asthma*** (cumulative)" – a positive response to the question: Has this child ever had asthma diagnosed by a doctor?;;

2) "***incident asthma***" – a positive report of recent or new diagnosis for asthma in the last 12 month by physician or health professional; with no history of ever been diagnosed with asthma in the past;

3) "***current asthma***" – a positive report of at least one visit to a health professional for asthma treatment in the last 12 month or current wheezing symptoms in the last 12 months with a history of ever been diagnosed as having asthma by a doctor in the past; and

4) "***current wheeze***" – defined as a positive report of wheezing or whistling in the chest at any time in the last 12 months that is not associated with colds.

In the ongoing worldwide ISAAC study,[80] the standardized symptom questionnaire was based on several questions previously used in studies of children conducted in Australia,[82] England,[83] and New Zealand.[84]

1.6.2 Physiological Measures

Physiological measures of asthma include lung function measurement or a measure of both bronchial hyperresponsiveness (BHR) and symptoms of asthma that may include one or more of wheeze, chest tightening, and cough. Physiological measures are useful because they may define "clinically important" outcomes among children who might need better treatment than based on the presence of symptoms alone. Also, lung function and BHR may act as a standard measure to compare different studies. Exercise challenge testing has also been proposed and used in some populations.[85] Alternatively, measurements of serial peak expiratory flow (PEF) with or without exercise testing, may be carried out over a period of time to demonstrate expiratory flow variability among individuals.

1.6.3 Health Services and Medication Usage

Other measures of asthma morbidity used in some health service research studies include frequent hospitalization, medication usage, and quality of life indicators.[81] These may be important for determining the success of interventions.

1.6.4 Strengths and Limitations of Asthma Measures

In comparison to other measures of asthma, the use of symptom questionnaires is relatively inexpensive for conducting large population-based studies. Use of symptom questionnaires alone, however, may under- or over-estimate the prevalence or incidence of the disorder. Also, symptom questionnaires may suffer from inter-cultural, psychological, and sociological factors, and the resulting data may not allow different populations to be compared. For standardization, the ISAAC study suggested the use of video questions to overcome linguistic and cultural barriers.[80,81] Symptom questionnaires that are based on past events recall can also be influenced by recall bias. Although the use of physician-diagnosed asthma and medication data from health services may provide medical certification of the disorder, some children in the population may have asthma that may have gone undiagnosed. Therefore, the use of this measure could underestimate the true prevalence or incidence. Although the use of objective measures can provide more meaningful measure of asthma, they are time-consuming and costly, generally yield a low compliance rate, and are not feasible for children who are less than three years old. For instance, a lung function measurement is generally not practical for preschool children and the BHR may not be feasible for use in a larger scale, epidemiological survey.

1.6.5 Validation of Questionnaire for Reported Asthma

Validation of questionnaire instruments for measuring asthma morbidity is done by comparisons with a gold standard – usually physician examination.[78,81] Nevertheless, assessing each subject with a physician's examination may be impractical in large-scale population studies. More commonly, in population studies, lung function, BHR, or exercise testing is performed in random samples of both asymptomatic and symptomatic subjects, to validate the symptom questionnaire.[72] This remains as the principal validation method for large prevalence studies.[78,81] Although BHR testing is not specific to asthma, it provides a reliable marker of physiological characteristics associated with asthma.

In population studies, for validating survey instruments against a "gold standard," Youden's Index has been shown to provide the most appropriate measure of validity of a particular question or technique.[81] Recently, BHR was recommended to be used together with a symptom questionnaire to increase the reliability of symptom measures of asthma in population studies.[86] Nevertheless, a review of population-based studies that compared the validity of a symptom questionnaire and BHR testing to a clinical examination by a physician or a previous diagnosis of asthma, showed that an objective measurement such as the BHR alone or combined with a symptom questionnaire may not necessarily provide a more valid measurement than the symptom questionnaire alone.[78,79] When a symptom questionnaire was used alone to measure asthma, it had a higher sensitivity and higher Youden's Index in both children (13 to 14 years of age) and adults (28 to 44 years of age), than did the BHR alone, or the BHR plus a symptom questionnaire, when compared with clinical assessment by a physician.[78, 87] However, BHR has been found to have a high sensitivity (greater than 90%) when used to measure asthma in clinical studies of asthma.[88]

1.7 Epidemiology

The systematic review outlined in this section presents several factors associated with asthma and wheeze from cross-sectional and longitudinal studies that were identified in the EMBASE and MEDLINE databases via PubMed and Ovid interfaces.

1.7.1 Incidence and Natural History

A much clearer picture of the natural history of childhood asthma has evolved from several longitudinal studies of birth-cohorts conducted over the last two decades.[60,65,89,90] Lessons learned so far indicate that the development of asthma and wheezing illness are most common among children in the preschool years.[91] In some children, asthma symptoms seem to remit with time. Children who develop the disease and the disease show persistence throughout their lifetime are associated with more severe symptoms such as, increased airway reactivity, and loss of lung function later in life.[8] These children typically have family histories of asthma and demonstrate increased airway reactivity and atopy in childhood.[8,65]

In a longitudinal study to examine lung function among 243 infants, the 23 children who had air flow limitations were also found to have reduced lung function and increased airway responsiveness.[92] The majority of these children were diagnosed with asthma at the age of two years.[92] When infants who were enrolled in the Tucson Respiratory Health Study were assessed at the age of 6 years, approximately 51% had never wheezed. Of these, 20% who wheezed before the age of 3 years stopped wheezing by 6 years, 15% of the children who had no wheezing before the age of 3 years had wheezing at the age of 6 years, and 14% had wheezing both before 3 years of age and at 6 years of age.[60] Another study investigating which wheezy infants will continue to wheeze later in life found that wheezing was more persistent in children who had family histories of atopy.[93] Also, Rhodes *et al.*,[94] noted that remission of wheeze was common in children who were younger than five years of age, which was more likely if it had occurred on more than two occasions before this age, but that wheeze was likely to persist if it occurred at eleven years of age or older. In a national population-based birth cohort study of 11,486 children conducted in the UK, 80% of the children with wheezing at the age of 5 years did not wheeze at 10 years, and 50% of 238 children with asthma diagnosed at the age of 5 years did not have asthma symptoms at the age of 10 years.[95] In another UK study conducted among 67 infants who were evaluated annually through the age of 5 years, and then at the age of 11 years, of the 21 children with wheezing before 2 years, 76% did not wheeze at age 11 years, and 61% did not have bronchial hyper-responsiveness at this age.[89]

In summary, while most of these studies were designed to clarify the natural history of asthma and to describe the phenotypic phases of the disease, several questions relating to the role of genetic, environmental, or lifestyle variables in the development of these conditions still remain unanswered. Long-term follow-up studies are required to monitor the role of genetic, environmental, or lifestyle variables associated with the complex pattern of remission and relapse in wheezing infants and children that follow the children through adolescence and into adult life. Identifying the different phenotypic wheezing groups early in life and their associated risk factors would be helpful for developing public health interventions, aimed at reducing the severity of asthma symptoms and the loss of lung function among children who are at risk.

1.7.2 Prevalence and Geographic Variability

The prevalence of childhood asthma has been increasing worldwide with greater burden reported in developed countries.[96] Phase I of the International Study of Asthma and Allergy in Childhood (ISAAC), conducted in 91 centers from 38 countries, among 6 to 7 year olds; and in 155 centers from 56 countries, among 13 to 14 year olds,[14,15] represented by far the most extensive international survey of respiratory symptom for prevalence of asthma ever performed among children. The results from the study indicated that the prevalence of asthma ranged from 1.3% to 30.8% in younger children (6-7 year olds), and between 1.4% and 30.2% in older children (13-14 year olds). A lower prevalence of asthma was observed among countries such as Albania, Austria, Belgium, Estonian, Germany, India, Iran, Latvia, Poland, Russia, and Georgia; and a higher prevalence among countries such as Australia, Costa Rica and New Zealand. The study raised possibilities of race, culture, ethnicity, and environmental factors being risk factors for the development of asthma in children. Phase III of the ISAAC study, which was completed in 2002-2003, showed different regional patterns and trends in asthma symptom prevalence.[97] In comparison to the results from the Phase I of the ISAAC study conducted in 1992-1996, asthma symptom prevalence increased in Africa, Latin America and some parts of Asia and global differences in asthma symptom prevalence decreased in the Phase III.[97]

Also, in several studies conducted in the USA, self-reported prevalence of asthma were found to have increased by 73.5% (from 1980 to 1996), with an estimated 14.6 million persons reporting asthma attacks during the preceding 12 months.[12,17,98] The most substantial increase was found among children who were less than 5 years old (160% - from 22.2 to 57.8 per 1,000) and who were 5 to 14 years old (74% - from 42.8 to 74.4 per 1000).[12]

The prevalence of asthma among children in Canada has been reported to be 10% to 15%,[7] and some experts believe the figure to be as high as 20%.[99] Significant variation has been reported within, and among the provinces. In children (less than 14 years old), asthma prevalence was found to be slightly higher in the Atlantic region (14%) than in other regions of Canada (varying from 10% to 12% in Quebec, Ontario, the prairie provinces, and British Columbia).[100] The trends have increased across all Canadian regions, with the prevalence more than doubling from 1974 to 1995.[100] In the Canadian arm of the ISAAC study, an 11% asthma prevalence was reported in children, 6 to 7 years of age, living in Saskatoon, and a 19% prevalence was reported for an equivalent group living in Hamilton.[85] In school-based surveys of 28,029 students, 5 to 19 years of age, in 9 voluntary health units and departments across Canada, asthma prevalence varied between 10% and 18%, with higher rates reported in Prince Edward Island, Halifax and Kingston, while lower rates were reported in health unit areas in Sherbrooke, Guelph, Winnipeg, Saskatoon, Edmonton, and Kelowna.[101] In 1994, similar cross-sectional studies conducted among 5-8 year old children from 30 communities across Canada found that 4.7% of the 14,948 children who completed the surveys reported physician-diagnosed asthma.[30] Persistent wheezing was reported for

13% and persistent cough for 5.9% of the children. Asthma was most common in the two provinces the Maritime region (7.4%) and least common in British Columbia (3.3%) and Quebec (3.4%). Wide regional differences were noted for persistent cough, persistent wheeze, and hospital separation rates for asthma, which were approximately 800 per 100,000 for the Maritimes and 396 per 100,000 for British Columbia. These geographic differences persisted despite adjustments for several host and environmental (indoor and outdoor) characteristics.[30]

1.7.3 Asthma Hospitalization and Mortality

Studies conducted in the last two decades have indicated generally increasing rates of hospital admission for children in a number of countries.[102-105] Nevertheless, in a recent study conducted in the UK, hospital admissions which increased in the early-1960s, and especially among children until the late-1980s, have fallen,[20] even though the prevalence of wheeze during the previous year increased from 12.9% in 1991 to 17.8% in 2002.[104] The authors concluded that the absence of a corresponding increase in hospital service may reflect a more widespread use of prophylactic treatment or changes in the use and provision of medical services.[104,105]

1.7.4 Risk Factors

Risk factors, presented in this section, are sub-categorized into: i) prenatal and perinatal factors; ii) individual host and socio-demographic factors; iii) early life factors (and familial, genetic, and socio-economic factors); and iv) neighbourhood factors. These variables have been reported in the literature as being associated with asthma or wheezing conditions.

1.7.4.1 Prenatal or Perinatal Factors

Maternal smoking during pregnancy is an important factor that has been shown to be a prenatal risk factor for reported asthma and wheezing during early childhood, independent of postnatal environmental tobacco smoke (ETS) exposure.[106] For wheezing, from 18 to 30 months of age, light smoking during the third trimester of pregnancy appears to confer the same risk as does heavier smoking.[107] Furthermore, *in utero* exposure to tobacco may affect airway responsiveness, cause sizeable adverse effects on neonatal lung mechanics and reduce the infant's airways after birth.[108] In a German study of allergy and asthma, exposure to tobacco smoke *in utero* was an important risk factor for asthma in school-age children.[109] Similarly, in a large British cohort,[110] children whose mothers smoked during pregnancy and continued to smoke until the children were 16 years old were at a significantly greater risk of asthma than were their counterparts whose mothers had never smoked. Also, maternal smoking is associated with small deficits in lung function in school-aged children. However, distinguishing between residual effects of maternal smoking during pregnancy and childhood ETS exposure to explain these deficits is difficult.

Maternal alcohol intake during pregnancy has not been shown conclusively to be a risk factor for the development of childhood asthma.[111] Maternal alcohol during pregnancy was considered a potential confounder in a longitudinal study assessing the relationship between maternal smoking and behaviour problems in children.[112] Other prenatal factors implicated as potential risk factors for early development of asthma among children include: *maternal use of antibiotic prescription medication*, *infection in* *pregnancy*, *maternal depression*, *complicated delivery*, *caesarean delivery*, and *maternal prior history of contraceptives usage*.[113]

In several studies, *young maternal age* was reported to be associated with an increased risk for development of childhood asthma or wheezing especially among infants and toddlers;[114-117] however, this association is not clear for young paternal age. Martinez *et al.* showed that young motherhood is an important risk factor for wheezing illnesses during the first year of life and the incidence of physician-diagnosed and wheezing significantly decreased with increasing age of mother at birth.[118] A similar finding was obtained from the second National Health and Nutritional Examination Survey.[117] The significant effect of maternal age suggests that the *in utero* environment may be an important determinant of asthma.

1.7.4.2 Individual Host, Socio-Demographic, and Early Life Factors

Viral respiratory tract infections (VRTI) are associated with wheezing illnesses in children of all ages. Respiratory syncytial virus (RSV) has been recognized to cause most of the early respiratory tract infections among children in early life.[119-121] Statistically, this has accounted for more than half of all respiratory tract illnesses present in childhood.[121] From recent studies, VRTI caused by parainfluenza virus (PIV), and picornavirus (rhinovirus/enterovirus) identified by reverse transcription-polymerase chain reaction (RT-PCR) testing have been shown to be related to the first episode of wheezing in children who go on to develop chronic asthma.[122,123] The prevalence data reported from the Tucson Respiratory Child Study indicated that 32% of children may experience wheezing with VRTI in their first year of life.[8] Nevertheless, whether such infections play a causal role in the development of asthma is less clear.

While asthmatics are more likely than others to wheeze in early life, the majority who wheeze with early VRTI do not develop asthma later in life. Hence, the etiologic role of VRTI in the development of asthma is not clear. The results from a recent study, however, show that a history of bronchiolitis or croup in early childhood is predictive of BHR, thus suggesting that VRTI may play an etiological role in the development of childhood asthma.[124]

While acute sinus infections and common cold can trigger acute symptoms of asthma,[123] some recent studies have proposed that repeated infections with other common childhood viral pathogens may help the immune system to mature so as to prevent the onset of allergic diseases including possibly asthma.[36,123,125] Evidence from current studies supports the idea that children who have an increased likelihood of respiratory infection from exposure to older siblings, early daycare attendance, or dwelling in a farm residence, may have protection from developing asthma in early life.[44,45,47,49,53,54,57,126, 127] On the other hand, respiratory infections with certain intracellular pathogens, such as chlamydia and mycoplasma, may cause acute and chronic wheezing in some individuals.[3] Other medical conditions that occur early in childhood, such as pneumonia, whooping cough, chronic bronchitis, recurrent abdominal pain, and migraine, have all been implicated with the development of asthma later in life[110,128,129]

To date, asthma in children has remained primarily a wheezing disease, but not all children who wheeze continue to develop asthma at a later age. The role of early wheezing as a risk factor, independent of respiratory tract infection, for the development of asthma is still unclear. Although studies have identified an association between early wheezing and risk for atopy in childhood,[130-132] the evidence for an independent association with asthma is not conclusive. Recently, the role of wheezing without respiratory tract infection in early life and the development of asthma later in life was investigated in several studies.[58,60,61] By predicting the incidence of asthma from a baseline history of wheezing in infants and toddlers, it may be possible to determine the prognosis and development of intervention early in life.

In ~~a~~ recent review, the effect of *age* on the development of asthma and wheezing symptoms had a characteristic correlation with a strong peak among preschoolers (< 5 years), that declined in the adolescence years.[91] Among the 19 studies that reported the incidence of physician-diagnosed asthma in childhood, presented in the review,[91] the trend in the rate of occurrence of asthma for children, less than 19 years of age, decreased from 29.5[133] per 1,000 persons (among infants and toddlers) to 0.6 per 1,000 persons (among teenagers).[134]

Sex is an important demographic factor associated with symptoms and prevalence of asthma, and appears to be related with age. In several studies, young boys have shown a greater risk of developing asthma before the age of 14 years, than girls.[117,135-137] Nevertheless, young teenage girls experience more deficiencies in their pulmonary function than do boys.[138] The reason for the early increased risk among young boys is not clear but may be related to smaller airways relative to lung volumes, and a higher prevalence of atopy in boys. This relationship later reverted with girls having higher rates than boys when in their adolescence years. The greater risk for adolescent girls may be due to hormonal changes in puberty.[138,139]

Low birth weight (LBW<2500 grams)[137,140] and *pre-term birth* (before 28 weeks)[114] have been reported as risk factors for the incidence of asthma among children. In a cross-sectional analysis of 5,672 children, low birth weight was significantly associated with both asthma and wheeze for children under 11 years of age.[117] While pre-term and full-term children do not differ in terms of atopic sensitization, some authors have reported an increased prevalence of cough and wheeze, and a reduction in lung function, in children and adolescents born prematurely or with low birth weight. In a study of the relationship of birth weight and childhood respiratory infection in the development of lung function later in life, LBW was found to predict lower than average values of FEV_1 in adulthood, independent of smoking, age, social class, or lower respiratory tract infection.[141] In another study of 5,573 children (5 to 11 years of age), respiratory symptoms (especially wheeze) were found to be significantly associated with gestational days, and an extra week of gestation reduced the risk of severe wheeze by about 10%. This association was not observed for birth weight,[142] although lung function was related to birth weight and not gestational period.

Breastfeeding has been reported to reduce the risk of atopy and asthma,[128,135,143] although the evidence is conflicting.[144,145] Some studies suggest that the relationship between childhood asthma and breastfeeding may depend on the propensity for atopy and the history of maternal asthma.[146,147] In 1,246 newborn infants, who were followed for 13 years, children with asthmatic mothers were significantly more likely to have asthma if they had been exclusively breastfed.[147] This relationship was only evident for atopic children and persisted after adjusting for confounders. In contrast, the relationship between recurrent wheeze and breastfeeding was age-dependent. Exclusive breastfeeding, however, was associated with significantly lower rates of recurrent wheeze, regardless of the presence or absence of maternal asthma or atopy in the child.[147]

Evidence has emerged that *family size, having more siblings, and daycare attendance* may reduce the risk of atopic diseases including asthma, among children.[31,54,57] While the likelihood of infection exposure, associated with these factors, has been suggested to be a possible mechanism explaining this protective effect, some recent studies suggest that other factors, such as fetal life and the maternal endocrine system during pregnancy, may be involved.[148,149] In a recent review, large families may be associated with reduced atopic diseases including eczema, hay fever, and allergic sensitization, though the evidence for asthma could not be confirmed.[126] Unlike the sibling effect, the reduced association indicated for daycare attendance and asthma could not be confirmed in some studies.[150] In a review of the findings from eight studies, many discrepancies were found, and a definitive conclusion could not be made about whether or not daycare attendance reduces the risk of asthma.[127] A possible explanation for these inconsistencies may be in the ambiguities that surround the definition of asthma, especially during infancy and early childhood, which can easily lead to misclassification.[125] Also, the causes of such inconsistencies may be due to the cross-sectional nature of these studies or the variant methodology used to define daycare attendance, which may include different types of exposure that were not clearly determined.

Personal history of *atopy* is one of the strongest factors associated with an increased risk of persistence and severity of asthma, independent of a parental history of asthma and allergy.[1,91] Atopy is characterized as a positive response to the application of a specific allergen in skin-prick testing,[81] and asthma is strongly related, although these may also occur independently of each other.[1] More than 80% of the asthma that occurs in children and young adults is associated with atopic sensitization, and only about 20% is not.[1,81] In a birth cohort study of children with family histories of asthma, high levels of IgE, measured at 6 months, was a strong predictor of a child's onset of asthma at 3 years, and associated with the development of asthma between the ages of 6 and 8 years.[151] In susceptible infants and toddlers, atopy is suggested to predispose the airways to sensitization by environmental allergen or irritants, leading infants to experience recurrent symptoms of asthma.[1] In particular, early exposures to domestic dust mites, alternaria (a group of fungi), or animal allergens were shown to play an important role in the development of asthma and wheezing conditions. In a study of environmental allergen sensitization in children, BHR on inhaled methacholine was seen to be positively correlated with skin test positivity to alternaria, and cat and dog allergens.[152]

Dietary components may also play an important role in food allergies or even cause food-induced lower airway reactions, but this association with developing asthma is not clear. In several studies, allergic sensitization to aeroallergens and food products, including milk, eggs, or peanuts, in infants and toddlers, was found to be a significant predictor of asthma.[152-155]Although studies from Australia reported that a high intake of oily fish was associated with a lower prevalence of current asthma among children, the finding could not be confirmed in double-blind studies with a fish oil supplement diet for individuals with asthma or allergies. Nevertheless, an association was found between fish consumption and improved baseline FEV_1.

Only a few studies have reported an association between *race/ethnicity* and the development of asthma.[91,156,157] The prevalence of asthma in the US has been shown to be disproportionately higher in minority groups such as Blacks and Hispanics.[117] In a recent Canadian study, the incidence of wheeze and asthma prevalence appeared to be significantly greater in non-Aboriginal children than in Aboriginal children.[156] Aboriginal children in an Australian study, however, were found to have a significantly greater risk of physician-diagnosed asthma by six years of age.[128] Also, Gillilan *et al.*[158] reported that non-Caucasians were at a significantly greater risk of physician-diagnosed asthma by the age of 18 years. Similar racial/ethnic disparities were evident from cross-sectional data on 14,244 children (aged <18 years old) in the 1997 National Health Interview Survey.[159] In a recent study, a large proportion of the racial/ethnic differences for asthma prevalence were explained by factors related to income, area of residence, and level of education.[160] Hence, any excess risks that may be attributed to a racial or ethnic group, for the development of asthma, should be determined with caution. A group that may be at risk, such as the very poor or those with low socio-economic status, may be associated with race/ethnicity, which can confound any association that might be established from other studies.[159] In any case, the wide variation of lifetime prevalence of asthma among countries in the ISAAC study[15] raises the possibility of race, culture, and ethnicity being risk factors for asthma, independent of other factors.

In recent years, evidence has suggested that *psychological factors* may be associated with the development of asthma.[161,162] In 1993, a workshop was sponsored by the Division of Lung Disease of the National Heart, Lung and Blood Institute, to understand the influence of psychological factors in the development of asthma.[163] In the National Cooperative Inner-City asthma study, conducted in the US, asthmatic children had more behaviour problems, compared to a normative sample, and their caregivers had elevated levels of psychological distress.[164] In a recent birth cohort study, asthma in adolescence and young adulthood was associated with an increased likelihood of major depression (OR 1.7, 95 % CI 1.3-2.3), panic attacks (OR 1.9, 95 % CI 1.3-2.8), and anxiety disorder (OR 1.6, 95% CI 1.2-2.2).[165]

Obesity, as determined by body mass index (BMI) has been shown to be a risk factor for asthma.[166,167] In a cross-sectional study of 9,357 children (5 to 6 years of age), a dose-response relationship was found between BMI and asthma among girls with an adjusted odds ratio 2.12 (95% CI 1.22-3.68) for overweight children (BMI: 90th to 97th percentile) and 2.33 (95% CI 1.13-4.82) for obese children (above 97th percentile).[168] In this study, however, no significant association was found between BMI and asthma in boys. Also, in a ten-year follow-up study of healthy children in Denmark, high physical fitness was associated with reduced risk for the development of asthma.[112]

1.7.4.3 Parental Factors

Evidence for a *hereditary* contribution to the development of asthma and wheezing among children has been noted for many years in the literature.[5,169] Several studies have shown that the occurrence of childhood asthma is clustered within families with parental histories of atopy, indicating an important genetic component in the development of the disease. A maternal history of asthma is the most important predictor of childhood asthma.[56,169] Millar and Hill[100] reported that if a child's mother had asthma, the child was 2.76 times more likely to develop asthma, however the odds ratio was reduced to 1.99 when the father was asthmatic, and increased to almost 3.0 when both father and mother had asthma.

Parental smoking or ETS has been reported to be an independent risk factor for the development of asthma and atopy among infants,[107,114,170-173] particularly, if the mother is a smoker.[174] Evidence supporting a causal role for ETS exposure comes from the small but significant effects of paternal smoking when the mother does not smoke. Nevertheless, not all studies have demonstrated this effect. In a recent longitudinal study, when the relationships between prenatal and postnatal tobacco smoke exposure and infant wheezing illnesses were compared in two geographically defined populations in the UK and the South Moravian Region of the Czech Republic,[106] among the children from the UK, maternal smoking during pregnancy was a risk factor for reported wheeze during early childhood, but smoking exposure after birth was not. In contrast, among children from the Czech Republic, a significant relationship was seen between infant wheeze and ETS exposure, but not with maternal smoking during pregnancy.[106] Parental smoking status by itself may become a less valid indicator and information regarding self-reported behaviours to protect children are needed. Moreover, these self-reports will need to be validated by biomarkers of children's actual exposure to offset socially desirable but inaccurate questionnaire responses.

Several *socio-economic* factors are reported to have an association with childhood asthma, including: parental education, occupation, and family income.[117] In a recent study, children of parents with low literacy level had greater severity of asthma outcomes (e.g., emergency department visits, hospitalizations, and days missed from school) than their counterpart of high literacy level, even after adjusting for asthma-related knowledge, disease severity, medication use, and other socio-demographic factors.[175] Still, evidence for the role of socioeconomic factors and the incidence of asthma is lacking. In a recent review of risk factors for the development of asthma and wheeze,[91] no prospective study was identified in the literature that assessed the role of socioeconomic factors in the development of asthma.

In a birth cohort study, *parenting difficulty*, measured at 3 weeks after birth, was a significant predictor of a child's onset of asthma at 3 years, and was later associated with asthma between the ages of 6 and 8 years.[151] In this study, parenting difficulty was measured using a standardized scale, which included assessment of maternal effect and coping, relational skill and social support, and sensitivity and responsively to care giving. High correlations were also found with postpartum depression and quality of relationship scales. An increased risk of asthma exacerbation was also associated with children from families with *single parent status*.[176]

1.7.4.4 Household and Environmental Factors

Several household and environmental factors have been shown to be associated with the development of children's respiratory health.[177-179] Independent of the burden of ETS, indoor pollutants, allergens such as house dust mites, cockroaches, animal dander, and insect matter (especially cockroach), rats, home dampness, and molds have been strongly associated with increased severity of respiratory symptoms and the development of asthma among children. Evidence to relate the risk of asthma to fumes from gas cooking is still unconfirmed.

Studies investigating *outdoor environments* have reported significant associations between outdoor air quality and asthma prevalence and morbidity.[170,177,180] Strachan found that differences between outdoor air quality pollution for urban and rural areas was associated with asthma attacks.[170] For pediatric patients (5 to 12 year old group), asthma-related emergency department visits in the Washington DC area of the USA, were significantly associated with the outdoor ozone concentrations.[180] In the study, an increase of 0.01 ppm in the ozone concentration explained a 3.2% increase in daily ED visits and an 8.3% increase in daily ED admissions.[180]

Differences in the prevalence of asthma and asthma-like symptoms in both children and adults have been associated with *urban and rural living*.[38,40,43,44,46,47,49,51] In particular, a reduced risk was reported for children dwelling in rural environments, and this was attributed to an increased likelihood of microbial infection in this environment, especially from farm environments with cattle and poultry.[53]

House ownership, closely related to socioeconomic status, was a significant predictor of persistent wheeze in a longitudinal study.[114] Region of country, housing age, and crowding were considered to be predictors of asthma in a cross-sectional survey of 4,164 children in the US (6 to 16 years of age).[181]

Various studies have demonstrated *seasonal variations* in hospital admissions for asthma, with significant peaks in September and early-October, compared with a small peak in April-May.[182-184] Different factors, associated with varying *climatic conditions* such as weather, pollens, viral infections, house dust mites, and fungal spores with seasonal elements, may account for the observed temporal variation in asthma exacerbation among children.

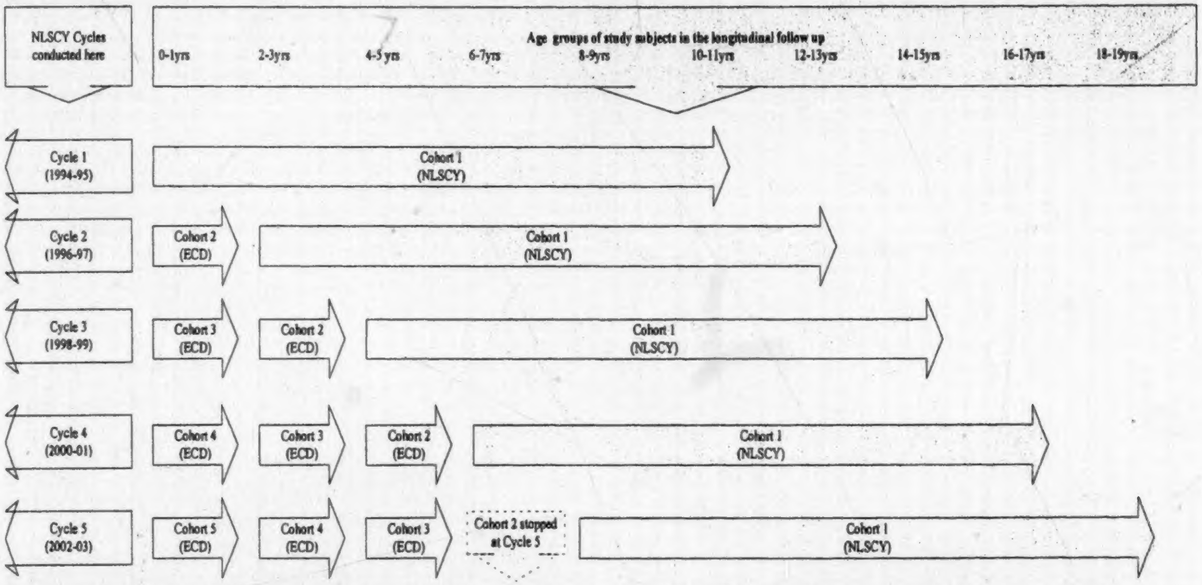
1.8 Summary of Literature Review

In summary, asthma is a complex genetic disorder recognised clinically by variable airflow obstruction and characterized by chest wheezing, airways inflammation, and reversible airflow obstruction. Challenges still exist in defining asthma, especially among young children. The relative roles that may be played by both genetic and environmental factors in the onset of the disease are still in need of elucidation. A number of studies have indicated that immunologic markers are the strongest predisposing factors for childhood asthma.[110,137,185,186] Others have shown that the development of asthma and wheezing at a young age is associated with family composition,[54,57] environmental tobacco smoke,[137, 171] low family income or socio-economic class,[26,117,187] crowding,[188] sensitivity to allergen exposure,[39,133,189,190] daycare attendance,[31,54] hereditary factors,[172,191] farm residence,[40,49-51,53,192] and male sex.[191] Nevertheless, most of these findings were obtained from cross-sectional studies conducted mainly to understand associations and to generate hypotheses. Few longitudinal studies have been conducted to reveal the epidemiological risk factors or to provide clues for understanding the cause and the pattern of risk for developing asthma and related morbidities. Large-scale population-based longitudinal studies, such as the NLSCY, that cover large geographic areas, are needed to evaluate potential etiologic roles of prenatal and early childhood factors, for the purpose of designing public health interventions.

1.9 Ethics Approval

The proposals for each analysis in this thesis were reviewed and approved by Human Resource and Development of Canada (HRDC) for accessing the confidential, 'master' NLSCY Cycles 1 to 5 files (Statistics Canada), at the Research Data Center (RDC), University of Alberta. Also, the Health Research Ethics Board (HREB) at the University of Alberta approved this study (see Appendix for supporting documents).

1.10 Figures


NLSCY Cycles conducted here
Age groups of study subjects in the longitudinal follow up
0-1yrs
2-3yrs
4-5 yrs
6-7yrs
8-9yrs
10-11yrs
12-13yrs
14-15yrs
16-17yrs
18-19yrs
Cycle 1 (1994-95)
Cohort 1 (NLSCY)
Cycle 2 (1996-97)
Cohort 2 (ECD)
Cohort 1 (NLSCY)
Cycle 3 (1998-99)
Cohort 3 (ECD)
Cohort 2 (ECD)
Cohort 1 (NLSCY)
Cycle 4 (2000-01)
Cohort 4 (ECD)
Cohort 3 (ECD)
Cohort 2 (ECD)
Cohort 1 (NLSCY)
Cycle 5 (2002-03)
Cohort 5 (ECD)
Cohort 4 (ECD)
Cohort 3 (ECD)
Cohort 2 stopped at Cycle 5
Cohort 1 (NLSCY)

The larger arrows represents the original longitudinal cohort (NLSCY), age 0 to 11 years at Cycle 1 and in Cycle 5 they were 8 to 19 years old. They will be followed till they are 25 years old. The smaller arrows represents the 0 to 1 year old early child development (ECD) cohort introduced at subsequent NLSCY cycles.

* Figure adapted from the "NLSCY Cycle 5 Micro data User Guide:" with modification[32]

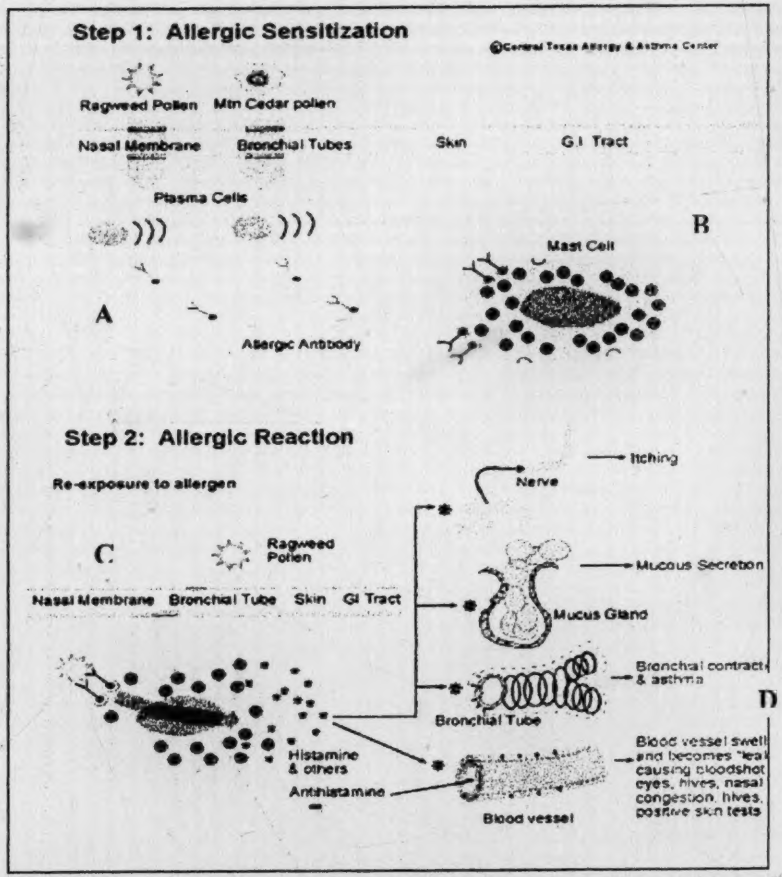
Figure 1.1 Description of the NLSCY and the ECD samples from Cycle 1 to Cycle 5*

A

In the allergic sensitization phase (**Step 1**); exposure to allergen initiates the production of allergic antibodies (IgE) by plasma cell of the immune system.

C

With re-exposure to allergen (**Step 2**), a reaction occurs and the IgE attached to the mast cell binds to the allergen as well. This result in degranulation of the mast producing immediate reaction due to the direct effect of the chemical (histamine and others) release from the mast cell on the muscle, blood vessels, mucus glands, and nerves of the bronchioles.


Step 1: Allergic Sensitization
©Central Texas Allergy & Asthma Center
Ragweed Pollen
Mtn Cedar pollen
Nasal Membrane
Bronchial Tubes
Skin
G I Tract
Plasma Cells
A
Allergic Antibody
B
Mast Cell
Step 2: Allergic Reaction
Re-exposure to allergen
C
Ragweed Pollen
Nasal Membrane
Bronchial Tube
Skin
GI Tract
Histamine & others
Antihistamine
Nerve
Itching
Mucous Secretion
Mucus Gland
Bronchial contract & asthma
Bronchial Tube
D
Blood vessel swell and becomes "leak causing bloodshot eyes, hives, nasal congestion, hives, positive skin tests
Blood vessel

B

The IgE travel through the blood stream and attaches to the mast cell lining the respiratory tract.

D

A late phase response occurs a few minutes later and is due to the influx of cells, especially the eosinophils, to the lungs. These cells are attracted to the site by chemical release by mast cell degranulation. The influx of these produces the inflammation and symptoms characteristics of asthma

This figure was adapted from ***Central Texas Asthma and Allergy Center*** *website: www.centraltexasallergy.com/patiented.shtml*). Assessed March 22, 2007. See Lieberman P (1999)[1] for reference to text in **A, B, C, & D.**

Figure 1.2 The allergic reaction and it relationship with asthma: 1) the sensitization phase; and 2) the reaction phase.

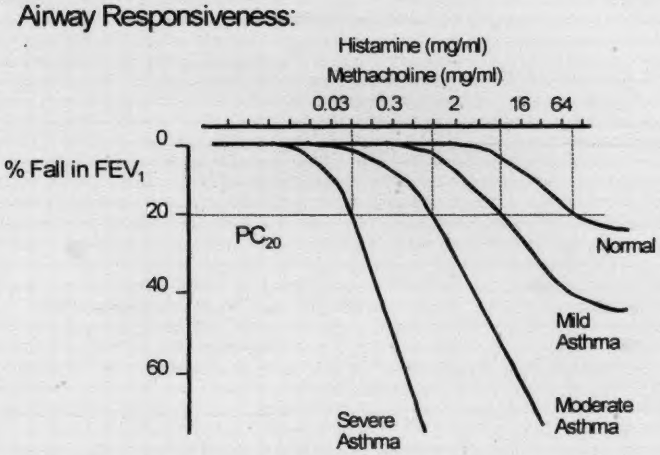


Figure 1.3 Classification of asthma severity by responsiveness to a bronchial challenge test

1.11 References

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Chapter 2

Reduced Risk of Physician-diagnosed Asthma among Children Dwelling in Farming Environments[*]

2.1 Introduction

Asthma is a common chronic condition among children and adults. Several cross-sectional studies have suggested that residing within a farm environment reduces the risk of allergic diseases among children[1-5] and adults.[6] Other cross-sectional studies have shown that early childhood exposure to a farm environment may reduce the risk of asthma and allergic sensitization during adulthood.[7,8] Children living in farm environments had a lower risk of hay fever, allergic sensitization and/or asthma in studies conducted in Switzerland,[1] Austria,[2] Germany,[3] and New Zealand.[4] In cross-sectional studies conducted in Canada, children and adolescents residing on a farm had a lower prevalence of asthma and atopy than did non-farm counterparts.[5,9] The "hygiene hypothesis" has been proposed as a possible explanation for lower proportions of asthma and allergy among rural and farming populations and for higher proportions among urban populations.[10,11]

Despite knowledge of the associations observed in these studies, it was not possible to ascertain whether or not exposures preceded the development of asthma, due to the cross-sectional nature of these studies. Accordingly, the current study was conducted prospectively to investigate the protective effect of living in farming environments on the incidence of asthma among children after adjusting for several independent confounding factors that were available at baseline. The study sample was drawn from the National Longitudinal Survey of Children and Youth (NLSCY) conducted in Canada.[12] To date, no prospective longitudinal study has been conducted to examine the relationship between developing childhood asthma and living in farm environments.

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[*] A version of this chapter has been published: Midodzi, *et al* 2007; Respirology

2.2 Methods

2.2.1 Cohort and Study Design

The details of the NLSCY have been published elsewhere in the micro-data user's guide.[12] An overview of the NLSCY data is also provided in this thesis (Appendix A; Tables 6.2 and 6.3). Of the 16,903 children indexed in Cycle 1 (1994/1995) as the main longitudinal cohort, 15,648 were followed-up in Cycle 2 (1996/1997) with a response rate of 91.5%. For the present analysis, all children who had histories of asthma and wheeze at Cycle 1 and whose parents failed to complete the question about physician-diagnosed asthma in Cycle 1 or Cycle 2 were excluded. These exclusions left 13,524 children from 9,441 households for the analysis. At each cycle, the questionnaires sought information about children, parents, and household characteristics.

2.2.2 Outcome and Independent Variables

In the NLSCY, possible responses included asthma and other chronic conditions. For the outcomes used in this study, the PMK was asked: "Does this child have asthma that has been diagnosed by a Health Professional?" An affirmative response to this question at Cycle 2 was used to determine the incidence of asthma. This question was followed by questions on wheeze and asthma attacks in the last 12 months.

The main exposure variable was the neighborhood environment of each household, as reported at Cycle 1. Classifications were provided by trained interviewers from Statistics Canada who conducted the NLSCY using the following close-ended question: "Based on street level frontage, how would you characterize land use on this block/road?" (See Appendix A for list of classifications of the dwelling environments) Except for the responses: "primarily rural, farming" and "primarily rural, residential," all other responses were grouped into a new category ("non-rural"), which resulted in three categories for the study variable – "primarily rural, farming," "primarily rural, non-farming," and "non-rural". In the current study, these three categories are referred to as: farming, rural non-farming, and non-rural environments. Of the 9,441 households that were considered in this analysis, 10.5% were from rural farming environments, 8.1% were from rural non-farming environments, and the remaining (81.4%) were from non-rural environments.

Several other baseline factors were selected after reviewing an extensive list of epidemiologic studies on known risk factors for asthma and wheeze.[13,14-17] The factors considered in this study included: age, sex, individual history of physician-diagnosed or food allergies, number of visits to physician or pediatrician in the past 12 months, health status, maternal age at birth, presence of older siblings, family history of asthma, immigrant parent, parental smoking, home needing repairs, socio-economic status (SES) and geographic region. A dwelling unit was said to be needing repairs if major or minor repairs were required at the time of the survey. A crowding index was derived from the number of persons per bedroom in the household (See Questionnaire Table for each variable in Appendix A). An index of SES was derived by Statistics Canada[18] for each child, based on parents' occupation, educational level, and economic position. The information for country of birth and ethnicity of the children was collected in the survey but was not released to the researchers due to confidentiality concerns. A variable indicating whether or not a mother was a migrant to Canada was used as a surrogate for ethnicity.

2.2.3 Statistical Analysis

To account for the complex sampling design of the NLSCY, all statistical analyses were performed with survey data analysis (SUDAAN)-calculable procedures in the SAS software.[19,20] The survey responses used in the analysis were weighted using longitudinal weights provided by Statistics Canada at Cycle 2. Statistics Canada also provided 1,000 bootstrap weights for each child to account for the complex study design which included selection of more than one child from the same household.[21] These bootstrap weights were used in all statistical analyses including the univariate and multivariate analyses.

Initially, to determine the differences in the distribution of baseline risk factors between living environments as sources of potential confounders, bivariate tests of association were performed using chi-square statistics for categorical variable, and analysis of variance (ANOVA) for continuous variables. In the main analysis, the dependent variable was the outcome of asthma (presence or absence) and logistic regression was used to assess the association between the outcome and independent variables.[22] The variables that were significant in the univariate analysis were considered for the multivariate analysis. Interaction terms were examined between factors in the multivariate model and significant interactions were included in the multivariate model. As all parameter estimates and their standard errors were within a statistical expected range, hence there was no indication of co-linearity problem among the set of variables retained in the final multivariate model.

The bootstrap approach was used to obtain design-based variance for each parameter estimated in the logistic regression model. A description of the replication methods used in generating the bootstrap weights for the NLSCY is published elsewhere.[21] Briefly, several strata were derived, based on the sampling frame used for the data collection in the NLSCY. Within each stratum, a sample of primary sampling units (usually, the household) was chosen using random sampling with replacement. Bootstrap weights were obtained by adjusting the original sampling weight to reflect the probability of selection into the sub-sample. This method was used to ensure that, when a child was selected, other siblings from the same household was also included in the sub-sample. For the NLSCY survey, this process is repeated several times to derive a 1,000 bootstrap sample, and subsequently, the 1,000 bootstrap weights.

2.3 Results

2.3.1 Baseline Characteristics of the Study Sample

The sample cohort of 13,524 children was comprised of 1,461 (7.39%) from farming environments, 1,109 (5.67 %) from rural non-farming environments, and 10,954 (86.94%) from non-rural environments.

Table 2.1 shows the distribution of baseline characteristics of the cohort according to the three living environments. The distribution of age and sex, prevalence of childhood allergy and parental smoking, and proportion of mothers with ages of less than 20 years, at the time of the child's birth, were similar among the three living areas (Table 2.1). Children from the non-rural environment had significantly more visits to family physicians and pediatricians within the previous 12 months than did their counterparts from the rural environment. The Ontario region had the highest proportion of children living in rural non-farming and non-rural environments, whereas the Prairie region had the highest proportion of children living in farming environments. The proportion of children from single parent families was almost twice higher in non-rural environments, compared to the other two environments. The children from non-rural environments had the highest mean SES index.

2.3.2 Incidence of Physician-Diagnosed Asthma

The overall two-year cumulative incidence of asthma in Canadian children, less than 12 years of age, was 5.6%. Among the children with asthma at Cycle 2, 70.8%

reported an episode of wheeze in the previous 12 months whereas only 8.9% of the children without asthma reported an episode of wheeze in the previous 12 months. The incidence of asthma was significantly lower in children living in farming environments (2.3%) than in children living in rural non-farming (5.3%), and non-rural (5.7%) environments (Table 2.2).

The difference in asthma incidence between rural non-farming and non-rural environments was not significantly different. The incidence of asthma decreased with an increase in age and was higher in males than in females (Table 2.2). Among those living in farming and rural non-farming environments, asthma incidence was lower for children with a parental history of asthma compared to children without a parental history of asthma (Figure 2.1), however the differences between the two groups were not statistically significant. This pattern was reversed for children living in non-rural environments with higher asthma incidence for children who had a family history of asthma, compared to those who did not (Figure 2.1).

2.3.3 Univariate and Multivariate Results

In the univariate analysis, children from farming environments had a significantly reduced risk of asthma incidence in comparison to children from rural non-farming environments (Table 2.2). The unadjusted odds ratios (OR) for the association between living environment and asthma incidence were 0.41 (95% CI: 0.24 to 0.70) and 1.08 (95% CI: 0.74 to1.57) for children from farming and non-rural environments, respectively. The protective effect of living in a farm environment for the incidence of asthma observed in univariate analysis was reinforced in the multivariate analysis, even after controlling for potential confounders (Table 2.2).

2.3.4 Assessment of Interaction with Parental Asthma

In the subsequent analysis, the interaction between living environment and each of the significant factors in the multivariate model were examined, with only the interaction term between living environment and parental asthma being statistically significant (p=0.04). Table 2.3 presents the results of the final multivariate logistic regression analysis which included significant factors and the interaction term between parental history of asthma and living environment. The protective effect of living in a farming environment for asthma incidence was seen in children both with and without parental histories of asthma (Table 2.3). The protective effect was stronger when children had parental histories of asthma (OR = 0.22; 95% CI: 0.07 to 0.74), compared to when they did not (OR = 0.39; 95% CI: 0.24 to 0.65). This pattern was reversed for children living in non-rural environments. An increased risk of asthma incidence was seen for children living in non-rural environments, compared to children living in rural non-farming environments, with odds ratios of 2.51 (95% CI: 1.56 to 4.05) for children with family histories of asthma, and 0.96 (95% CI: 0.65 to 1.43) for children without family histories of asthma (Table 2.3). In addition to the living environment, male sex, child's allergy, one or more visits to family physician, home needing repairs, residing in the Atlantic region, and a higher SES and crowding index were significantly associated with the incidence of asthma (Table 2.3).

2.3.5 Sensitivity Analysis by Age Groups at Baseline

The multivariate analysis was repeated with the variables considered in Table 2.2 for age groups less than 2 year, 2 to 5 years, and 6 to 11 years. The protective effect of living in a farming environment for asthma incidence (compared to living in a rural non-farming environment), for the whole sample, was seen again in the stratified analysis with significant odds ratios in the age groups: less than 2 years (OR = 0.34; 95% CI: 0.13 to 0.91), and 2 to 5 years (OR = 0.20; 95% CI: 0.09 to 0.46), but not in the age group of 6 to 11 years (OR = 0.73; 95% CI: 0.33 to 1.63).

2.4 Discussion

2.4.1 Findings in Relation to the Farming Environment

In this Canada-wide population-based study, the two-year cumulative incidence of asthma was lower in children living in farming environments, compared to children living in rural non-farming and non-rural environments. The protective effect of living in a farming environment for asthma incidence was observed in children both with and without parental histories of asthma. On the other hand, living in a non-rural area was a risk factor for asthma, but only among those children with parental histories of asthma. It is possible that, the protective effect offered by dwelling in the farm environment might be related to endotoxin exposure through greater contact with farm animals and pets.[5]

In a study conducted in Northern Sweden, during the same period as this study, the two-year cumulative incidence of asthma was 1.7% among children 7 and 8 years of age,[23] which was lower than that observed for the Canadian children in the same age group (5.3%). Asthma prevalence has been reported to be higher in Western countries than in developing countries.[24] In several studies, this differential risk of asthma has been noted among urban and rural living environments, with a higher risk often reported for urban living.[25-27] These observed differences among living environments and geographic regions suggests that exposure to environmental factors are critical to the development of asthma. In this study, the use of rural non-farming environments in rural areas, as the reference, rules out the possibility that a decreased risk of asthma incidence in farming environments might be due to the increased risk of asthma observed in urban environments.[26]

The lower prevalence of asthma and/or other allergic diseases among farm dwellers has been reported in other cross-sectional studies conducted in Canada, Europe, and New Zealand for children,[1-4] adolescents,[5,9] and adults.[6-8] Children whose parents had farming as their occupation were found to have a reduced risk of sneezing attacks and atopic sensitization during pollen season, in a cross-sectional study conducted in Switzerland.[1] Children living in farm environments had a reduced risk of hay fever and asthma, and children who had regular contact with farm animals had a reduced risk of atopic sensitization in a cross-sectional study conducted in Austria.[2] In a cross-sectional survey conducted in Germany, the reduced risk for hay fever, asthma and wheeze was stronger for children whose parents were full-time farmers, compared to children whose parents were part-time famers.[3] In a cross-sectional study of 7 to 10 year old children, conducted in New Zealand, current farm residence was associated with an increased risk of allergic symptoms, whereas early-life animal exposures were associated with a reduced risk of hay fever, skin-test positivity, and asthma.[4] In the current study, children less than 2 years, and 2 to 5 year old had a stronger protective effect of living in a farm environment for asthma incidence, compared to children in the older age group of 6 to 11 years. These differences in the strength of protective effects between the age groups may be related to exposure to the farm environment including animals earlier in their life for the younger age group, in comparison to the farm exposure later in life for the older age group.

The hygiene hypothesis has often been cited as a possible explanation for the decreased risk of allergic diseases in farming and rural populations.[10,11,28] According to this hypothesis, a lack of early childhood exposure to infectious agents and oro-faecal pathogens results in insufficient production of T helper type 1 (Th1) cells which, in turn, increases the production of T helper type 2 (Th2) cells and results in increased risk of allergic diseases in children and adults.[29] In the current study, dwelling in a farming environment was associated with a lower incidence of asthma but not allergy. The lack of an objective measure to determine allergy in the current study could possibly explain the absence of association between farming environment and allergy. Skin-prick tests are used to determine allergy in most studies reporting reduced risk of allergy among children with farm exposure.[1,2,4]

In the current study, a significant interaction was observed between parental histories of asthma and the living environments. While the reasons for the observed difference between rural and non-rural environments in the effect of parental asthma on the incidence of asthma in children are not known, one could speculate. One possible reason for these observed results might be the higher prevalence of occupational asthma among parents residing in rural-environments, since their children are not at a higher risk genetically of developing asthma. This explanation seems unlikely, however, as a review article concluded that the prevalence of occupational asthma was not higher among farmers, compared to the general population.[30] Another possible explanation for these findings is that asthma among children living a farm environment might be Th1-mediated, rather than Th2-mediated, resulting in non-allergic asthma that might not be associated with parental asthma.[31] Also, these findings might be explained by the gene-environment interaction effect being protective for the development of asthma in a farming environment. In a study of adults, aged 20 to 44 years, from Germany, persons with the G299/I399 polymorphism in the Toll receptor (TLR4) gene had a lower risk of asthma prevalence associated with endotoxin levels in the house dust, compared to those without the polymorphism.[32] Further study using a population-based genetic method could be useful in exploring the findings from this study, in relation to dwelling environment, parental history, and asthma incidence in children.

2.4.2 Other Factors Associated with the Development of Asthma

In addition to dwelling environment and parental history of asthma, male sex, allergy, crowding index, SES indicators (SES index and home needing repairs) and residing in Atlantic region were significant factors associated with asthma incidence in my study. Male sex and allergy have been frequently reported as risk factors for developing asthma in children.[13] In this study, lower SES and home-needing repairs were significant risk factors of asthma incidence. In a case-control study, investigating risk factors of asthma in children, 7 to 9 years of age, in New Zealand, low socio-economic status, indicated by lower social class family or unemployed parents, was a significant risk factor for asthma.[33] A unit increase in crowding index was associated with a reduced risk of asthma incidence in this study. In a case-control study from Montreal, Canada, crowding in homes indicated by increased number of siblings, had an inverse relationship with asthma among children, 3 to 4 years of age.[34] In a case-control study from New Zealand, a dose-response relationship was observed between number of siblings and decrease in asthma prevalence among children, 7 to 9 years of age.[35]

The Atlantic region of Canada demonstrated higher asthma prevalence in a study that was based on the first cycle of the NLSCY[36] and in a cross-sectional study of Canadian children.[37] The finding was extended in this study, which also showed an increased risk of developing asthma in the Atlantic region. In a recent study,[38] chronic poverty among children in this region was investigated as a potential cause of these findings in the Maritime region, using the NLSCY data from the first cycle. No significant association was observed between chronic poverty and prevalence of asthma in the Maritime region.[38] In a study examining the relationship between severe asthma, as indicated by hospitalization and emergency department visits, with aeroallergens and air pollution levels, in 10 of the largest cities in Canada, no unusual relationship was observed in the two cities in the Atlantic region, compared to other cities in Canada.[39] Therefore, poverty and environmental factors do not seem to explain the increased risk of asthma in the Atlantic region. Similarly in a large scale population study of 14,948 children across Canada, physician-diagnosed asthma was reported for 4.7% of the children by their parents. Persistent wheezing was reported for 13%, and persistent cough reported for 5.9% of the children. Asthma was most common in the two Maritime provinces (7.4%), and least common in British Columbia (3.3%) and Quebec (3.4%). Regional differences were seen for persistent cough, persistent wheeze, and for hospital separation rates for asthma, which were approximately 800 per 100,000 in the Maritimes and 396 per 100,000 in British Columbia. Differences persist despite adjustments for several host and environmental (indoor and outdoor) characteristics. If confirmed by objective measures of asthma, detailed etiologic investigation could enhance our understanding of this phenomenon and of the major environmental determinants of asthma morbidity in general. Further research is required to elucidate the reasons for the increased risk of asthma in the Atlantic region.

2.4.3 Limitations

This study is not without limitations. First, cumulative incidence of asthma was based on parental reports of physician-diagnosed asthma in the interviewer-administered questionnaire. Also, there was no information on physician diagnosis available to assess the reliability of the parental-reported outcomes; as problem often arise with diagnosing asthma in young children. Nevertheless, a high proportion of children with asthma also reported an episode of wheezing in the previous 12 months, to indicate that the parental reports of physician-diagnosed asthma has acceptable validity. In addition, the parental-report is a commonly used method for determining asthma outcomes among children in other epidemiological studies. Second, interviewers' perception of the street level land usage in front of dwellings was used to determine farming or rural non-farming environments in rural areas. There was no information on ownership of pets, type of farm and farming activities collected in the NLSCY and were not assessed in the thesis. In addition, families may have also moved between the rural and urban areas within the two years of follow-up. The information on dwelling environments was not collected at the end of the follow-up in Cycle 2. Nevertheless, based on information on children's dwelling centers (urban metropolitan, non-urban metropolitan, rural) collected at both Cycle 1 and Cycle 2, over 99% of the children remained in the same dwelling centers during follow-up. Only the children with follow-up from the baseline to Cycle 2 were considered in this chapter. It is possible that, dwelling in farming environment would be more likely to be related to the development of asthma at Cycle 2 rather than at later cycles.

2.5 Conclusions

Notwithstanding these concerns, the current study indicates that children living in farming environments have a lower risk of developing asthma than children living in rural non-farming environments. This study extends results from previous cross-sectional reports on the prevalence of asthma, to asthma incidence in a longitudinal study.

2.6 Tables

Table 2.1 Distribution of baseline characteristics of the study cohort by dwelling environment

Characteristics	Total	Non-rural	Rural non-farming	Rural farming	p-value[‡]
Participants, N	13,524	10,954 (86.94%)	1,109 (5.67%)	1,461 (7.39%)	
Age, yr groups, (%)					
0 - 1	17.35	17.72	12.76	16.48	<0.008
2 - 5	34.38	34.39	34.80	33.86	
6 - 11	48.28	47.89	52.43	49.66	
Sex, (%)					
Male	50.01	49.84	51.26	51.10	0.69
Female	49.99	50.16	48.74	48.90	
Child allergy, (%)					
Yes	11.31	11.24	11.44	12.03	0.57
No	88.68	88.75	88.56	87.94	
Child's health status, (%)					
Rated low	9.08	9.07	8.91	9.39	0.96
Rated high	90.92	90.93	91.09	90.61	
No. of pediatrician visits, (%)					
None	74.20	72.38	86.63	86.14	<0.01
One or more	25.80	27.62	13.37	13.86	
No. of physician visits, (%)					
None	30.47	30.54	30.06	29.84	0.22
One	37.91	37.26	44.41	40.57	
Two or more	31.63	32.20	25.53	29.69	
Mother's age at child's birth, (%)					
Less than 20 years	3.21	3.23	3.62	2.68	0.55
Greater than 20 years	96.79	96.77	96.38	97.32	
Older sibling, (%)					
1 or more	44.72	45.92	38.89	34.95	<0.001
None	55.26	54.06	61.11	65.4	
Parental history of asthma, (%)					
Yes	7.50	7.59	8.54	5.81	0.02
No	92.50	92.41	91.46	94.19	
Single parent,, (%)					<0.001
Yes	15.22	16.36	8.52	6.3	<0.001
No	84.78	83.64	91.48	93.10	
Immigrant mother, (%)					
Yes	17.52	19.18	6.94	6.04	<0.001
No	81.20	79.45	92.35	93.25	
Either parent smokes, (%)					
Yes	34.40	34.16	36.11	35.95	0.001
No	56.75	56.44	58.44	59.13	
Home needing repairs, (%)					
Yes	23.60	22.13	29.30	36.69	<0.001
No	76.40	77.87	70.70	63.31	
Geographic region, (%)					
Atlantic	7.66	6.99	19.87	6.21	<0.001
Quebec	23.50	24.91	13.03	14.94	
Ontario	37.63	37.83	39.33	33.91	
British Columbia	12.60	12.85	14.27	8.24	
Prairies	18.61	17.42	13.52	36.69	
Body mass index, (kg/m^2), mean (sd)	18.22 (0.07)	18.22 (0.08)	18.32 (0.18)	18.26 (0.16)	0.34
Socio-economic index, mean (sd)	-0.07 (0.01)	-0.04 (0.01)	-0.18 (0.03)	-0.25 (0.03)	<0.001
Crowding index (no./room), mean (sd)	1.39 (0.01)	1.38 (0.02)	1.38 (0.02)	1.43 (0.03)	0.011

Only children with complete information were included in the analysis. All data are weighted by normalized longitudinal weights at Cycle 2. [‡] p-values were obtained using 1000 bootstrap longitudinal weights at Cycle 2

Table 2.2 Two-year cumulative asthma incidence and odds ratios for baseline risk factors from univariate and multivariate analyses

Baseline Factors	Incidence (%)*	Univariate analysis† Odds ratios (95% CI) §	Univariate analysis† p-value	Multivariate analysis ‡ Odds ratios (95% CI) §	Multivariate analysis ‡ p-value
Age, yr					
0 - 1	6.9	1.47 (1.10-1.97)	0.016	1.33 (0.89-2.00)	0.14
2 - 5	5.3	1.11 (0.83-1.47)	0.61	1.04 (0.81-1.33)	0.72
6 - 11	4.9	1.00		1.00	
Sex					
Male	6.5	1.49 (1.18-1.88)	0.001	1.54 (1.12-2.10)	0.012
Female	4.4	1.00		1.00	
Child allergies					
Yes	11.3	2.62 (1.91-3.60)	<0.001	2.35 (1.67-3.32)	<0.001
No	4.7	1.00		1.00	
Child's health status					
Rated low	7.6	1.52 (1.06-2.18)	0.02	1.23 (0.87-1.74)	0.21
Rated high	5.2	1.00		1.00	
No. of pediatrician visits					
One or more	5.87	1.12 (0.84-1.49)	0.429	1.15 (0.98-1.34)	0.07
None	5.26	1.00		1.00	
No. of physician visits					
Two or more	7.94	2.18 (1.16-2.95)	<0.001	1.84 (1.24-2.73)	0.007
One	4.63	1.23 (0.90-1.68)	0.201	1.24 (0.92-1.69)	0.139
None	3.80	1.00		1.00	
Mother's age at ch. birth					
Less than 20 years	8.6	1.72 (1.04-2.85)	0.04	1.46 (0.60-3.54)	0.36
Greater than 20 years	5.3	1.00		1.00	
Older sibling					
1 or more	4.7	0.71 (0.56-0.91)	0.007	1.18 (0.87-1.61)	0.25
None	6.4	1.00		1.00	
Parental history of					
asthma	11.4	2.52 (1.72-3.71)	<0.001	2.45 (1.65-3.62)	<0.001
Yes	4.8	1.00		1.00	
No					
Immigrant mother					
Yes	4.9	0.87 (0.77-0.98)	0.04	1.08 (0.63-1.87)	0.75
No	5.5	1.00		1.00	
Either parent smoked					
Yes	6.3	1.21 (0.95-1.55)	0.12	1.13 (0.76-1.69)	0.50
No	5.2	1.00		1.00	
Home needing repairs					
Yes	6.6	1.32 (1.00-1.74)	0.05	1.41 (1.00-1.96)	0.05
No	5.1	1.00		1.00	
Geographic region					
Atlantic	7.8	1.59 (1.19-2.12)	0.002	1.63 (1.09-2.44)	0.022
Quebec	4.9	0.95 (0.65-1.39)	0.79	0.96 (0.61-1.52)	0.85
Ontario	6.0	1.17 (0.85-1.60)	0.34	1.14 (0.79-1.64)	0.44
British Columbia	3.6	0.71 (0.46-1.10)	0.12	0.67 (0.44-1.00)	0.04
Prairies	5.2	1.00		1.00	
Dwelling environment					
Non-rural	5.7	1.08 (0.74-1.57)	0.68	1.19 (0.83-1.70)	0.30
Farming	2.3	0.41(0.24-0.70)	0.001	0.47 (0.35-0.64)	0.001
Rural non-farming	5.3	1.0		1.00	
Body mass index, (kg/m^2) ll	-	1.00 (0.98-1.02)	0.80	1.00 (0.99-1.02)	0.94
Socio-economic status ll	-	0.85 (0.73-0.98)	0.02	0.85 (0.71-1.01)	0.08
Crowding index	-	0.69 (0.52-0.93)	0.013	0.76 (0.53-1.07)	0.09

*Rates were weighted by normalize longitudinal weights at Cycle 2. † In the univariate analysis, each variable was included one at a time in the model ‡In the multivariate analysis, all the variables listed in the table were included in model. § 95% confidence interval and p-value were estimated using 1000 bootstrap longitudinal weight at Cycle 2. ll Cumulative incidence is not given for continuous variables.

Table 2.3 Final model including significant factors and an interaction term[*]

Risk Factors	Odds ratios (95% CI)[†]	p-value[†]
Sex		
Male	1.48 (1.15-1.91)	0.002
Female	1.00	
Child's allergy		
Yes	2.41 (1.73-3.35)	<0.001
No	1.00	
No. of physician visits		
Two or more	2.11 (1.55-2.88)	<0.001
One	1.31 (0.93-1.84)	0.12
None	1.00	
Home needing repairs		
Yes	1.36 (1.02-1.82)	0.03
No	1.00	
Geographic region		
Atlantic	1.52 (1.13-2.04)	0.005
Quebec	1.05 (0.74-1.49)	0.80
Ontario	1.18 (0.85-1.63)	0.32
British Columbia	0.64 (0.42-1.03)	0.07
Prairies	1.00	
Environment and parental history of asthma[‡]		
Presence of parental asthma		
Non-rural	2.51 (1.56-4.05)	<0.001
Rural farming	0.22 (0.07-0.74)	0.02
Rural non-farming	0.81 (0.21-3.16)	0.82
No parental asthma		
Non-rural	0.96 (0.65-1.43)	0.85
Rural farming	0.39 (0.24-0.65)	0.001
Rural non-farming	1.00	
SES index	0.83 (0.72-0.96)	0.01
Crowding index	0.65 (0.48-0.89)	0.007

[*] Complete observations were available for 11,751 children

[†] 95% confidence interval (95% CI) and p-value were estimated using 1000 longitudinal bootstrap weights at Cycle

[‡] Rural non-farming and no parental asthma was the reference category for all odds ratios

2.7 Figure

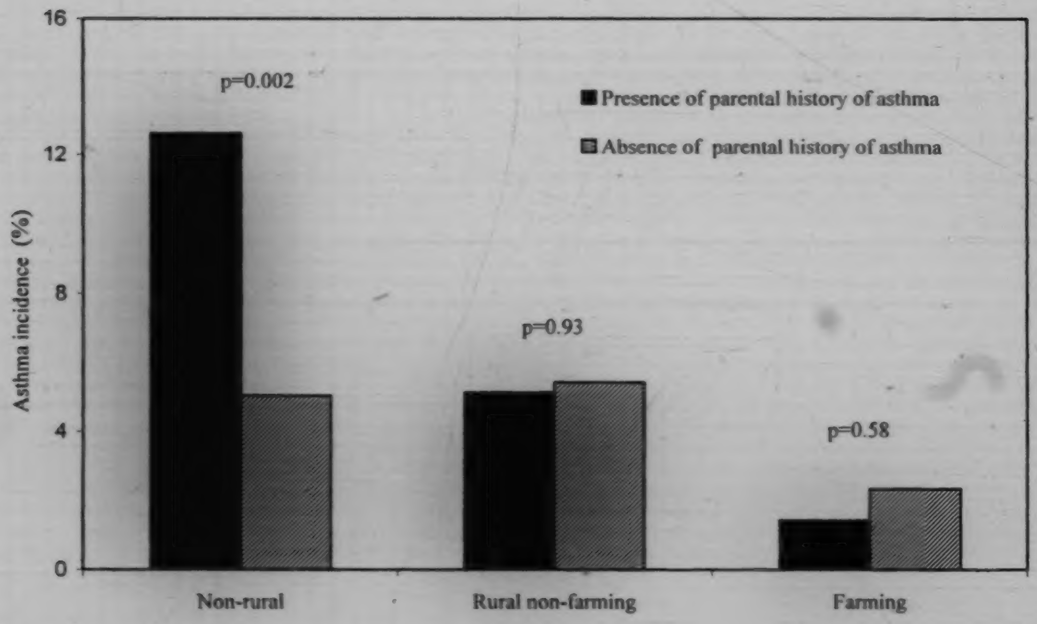

Figure 2.1 Cumulative incidence of asthma by living environment and parental history of asthma in Canadian children of ages less than 12 years. (The p-values in the figure were obtained from chi-square tests using the bootstrap weights.)

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Chapter 3

Early Childhood Factors Associated with Incidence of Asthma and Wheezing[*]

3.1 Introduction

Asthma is a common childhood illness and accounts for a significant burden and health care cost in most developed countries.[1] A recent review highlighted several factors that were associated with the development of asthma and wheeze among children and adults.[2] Although some risk factors were identified as being common to the development of both asthma and wheezing, several differences were also found. In early childhood, wheezing symptoms are very common,[3] however, identifying 'true asthma' early at this age presents a diagnostic challenge for physicians.[4] Lung function tests, often used to make a definitive diagnosis for asthma, are generally invasive and not feasible for infants and toddlers.[4,5] Therefore, the labeling of asthma among infants and toddlers requires careful consideration and must rule out other diagnostic possibilities associated with wheezing.[6]

Recent studies have identified an association between wheezing and atopy in early childhood,[7-9] though evidence for this association with asthma is not conclusive. Although wheezing among infants and toddlers could be transient, some children progress to severe and persistent respiratory symptoms before school age.[3,10] Predicting the incidence of asthma from a baseline history of wheezing in infants and toddlers may be important for prognosis and for development of intervention early in life.

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To date, few population-based longitudinal studies designed to understand the impact of early childhood factors on developing asthma and wheeze in preschool years have been conducted. Several studies have found an association between a lower prevalence of asthma and wheeze with children who have had environmental exposures early in life. In particular, an inverse relationship was found for increased microbial infection in childhood and the development of atopic diseases later in life.[11,12] Early childhood factors, such as daycare attendance, presence of siblings at birth, dwelling in rural communities (especially in environments associated with farming activities that increase the likelihood of infections), have been associated with a lower risk of developing allergic diseases including asthma.[13-18] Due to the cross-sectional nature of most of these studies, the exact time of occurrence of these exposures and the diseases is not known, hence, the factors identified in these studies have limited etiological importance for the development of asthma and wheeze.

The current longitudinal study used data from the Canadian Early Childhood Development cohort, which was part of the NLSCY, to investigate early environmental exposures occurring in the prenatal and postnatal period that are associated with the development of preschool (2 to 5 years) asthma and wheeze. The main objectives of this study were to: 1) investigate whether or not the occurrence of asthma and wheeze at the preschool age has different protective or risk factors suggestive of a different etiology, 2) assess the effect of early wheezing on subsequent development of asthma, after controlling for potential confounders, and 3) examine if factors that increase the likelihood of infections in early life, in particular, number of siblings at birth, early daycare attendance, and dwelling in non-urban areas, predict a lower incidence of asthma and wheeze.

3.2 Materials and Methods

3.2.1 The Early Child Development Study

The subjects enrolled in the ECD study were children aged less than 2 years at the baseline, dwelling in Canada. The ECD study was conducted as part of the ongoing NLSCY.[19] An overview of the NLSCY and the ECD data is given in Appendix A (Tables A.2 to A.6). The first two panels used in this analysis were conducted from 1996 to 2003. The subjects, indexed at baseline in Panel 1 (1996/97), were surveyed again in 1998/99 and in 2000/01. Similarly, the subjects, indexed at baseline in Panel 2 (1998/99), were surveyed again in 2000/01 and in 2002/03. Follow-up was terminated for Panel 1 in 2000/01 (NLSCY Cycle 4), and for Panel 2 in 2002/2003 (NLSCY Cycle 5) when the children were 4 to 5 years old for both panels. A sample of 8,940 children who had the person most knowledgeable as a biological parent and who provided complete information on the selected baseline factors were analyzed in this study.

3.2.2 Study Samples

The subjects included in this study sample were 8,499 children who had no prior history of asthma reported at baseline, and 5,919 children with no prior history of asthma and/or wheezing at baseline. These sub-samples were drawn for the analysis from the sample of 8,940 subjects who had biological PMKs, to provide complete information during follow-up. Because the children surveyed in Panel 2 were over-sampled by Statistics Canada, readjustments were made in the longitudinal weights to reflect the actual size of the target population for the ECD study. For instance, the Panel 2 sample, which was comprised of 5,905 children, represented only 49.3% of the subjects, while the 2,594 children selected from Panel 1 represented 50.7% of the study sample.

3.2.3 Study Outcomes

The main study outcomes were the incidence of physician-diagnosed asthma or wheezing at preschool age. These outcomes were determined at the first or second follow-up surveys which were conducted when the children were 2 to 3 years or 4 to 5 years of age, respectively. The time-to-incidence of each of these outcomes during the follow-up was calculated in months as the difference in age from the occurrence of the event and the age of enrollment. The children who did not report asthma or wheeze were considered censored at the termination of the follow-up. The censored time was calculated as the difference between the age at termination of the follow-up and the age at enrolment. Thus, the maximum possible survival time for each subject is 48 months from baseline.

3.2.4 Risk Factors

All potential risk factors selected for investigation in this study were obtained at baseline when subjects were less than 2 years old. The selected variables were based on factors that were perceived to be biologically important; as well as the prenatal and birth characteristics available on the ECD roster that had been cited in the literature as being associated with asthma and wheeze.[2,14-17,20-32] The selected characteristics at baseline included: presence of pregnancy health problems (i.e., history of diabetes or high blood pressure during pregnancy); maternal smoking during pregnancy; maternal age at birth; caesarean delivery; gestational age (<37 weeks); birth weight (<2500g); health status rated at birth; breast feeding (never, ≤ 3 months, or > 3 months); number of older siblings at birth; childhood allergy (diagnosed by a health professional); history of nose or throat infection; wheezing in the previous 12 months.

Other potential socio-demographic and parental factors that were considered include: sex; geographic region at birth (i.e., East {New Brunswick, Nova Scotia, Newfoundland, Prince Edwards Island}; Quebec; Ontario; Prairies {Manitoba, Saskatchewan, and Alberta}; and British Columbia (hereafter referred to as the West); parental atopy (history of asthma or allergies in either biological parent); parental smoking; score for household socio-economic status (SES); dwelling in either central metropolitan area (CMA) or non-urban and rural centers; and crowding index (derived as persons per bedroom in households greater than 1.5). The score for the SES was derived by Statistics Canada for each household, based on parents' occupation, educational level, and economic position. The overall household SES scores for the combined study sample ranged from -2.0 to 1.75. In this study, SES scores were categorized into four groups as follows: very high >1.0; high=1.0-0; low=0- (-1.0); and very low <-1.0. For sensitivity analysis, children with either biological parent having a history of asthma or allergies were considered "high risk" and children with both parents with no history of asthma or allergies were consider "low risk".

3.2.5 Statistical Analysis

To allow for the effect of time-dependency on outcome and baseline factors, due to the different entry points of subjects in the ECD cohort, a dichotomous variable to indicate the panels (coded as 1=Panel 1, 2=Panel 2) was considered in all analyses. Cox's regression[33-35] was used to account for the person-month of follow-up and to evaluate the effect of all predictors. All analyses were performed with the "TPHREG" procedure in the SAS statistical software (SAS institute, Inc, Cary, NC),[36] to estimate hazard ratio (HR) and 95% confidence intervals (CI). Normalized longitudinal weights were used to obtain design-based, finite population standard errors, as proposed by Binder[34] for survey data. Statistics Canada provided the longitudinal weights used to adjust for the probability of selection, non-response, and post-stratification for subjects selected in the NLSCY.

In the analysis, the primary aim was to identify the best set of risk factors, which led to the optimum prediction of incidence of asthma and wheeze in preschoolers before any biologically relevant variables were included in the study. Initially, bivariate analyses were performed to identify risk factors associated with the incidence of each outcome. Next, multivariate analysis was performed with modified stepwise methods[37] to obtain Akaike information criteria (AIC) for an optimal model to predict each outcome. See Shtatland *et al*[37-40] for a detailed discussion on the best model fitting approach using AIC. Because parental atopy and socio-economic factors may modify the association of environmental variable on incidence of asthma and wheezing, further assessment of the interaction of these variables was performed with all other variables retained in the final model.

3.3 Results

3.3.1 Characteristics of the Sample at Baseline

Table 3.1 describes the baseline characteristics for the sample for determining the predictors for incidence of asthma. In Table 3.1, 10.3% of the children were from single parent households, 27.4% had histories of asthma or allergies in either parent, 57.2% were breastfed for more than 3 months, 20.3% dwelled in rural non-CMA centers in Canada, and approximately equal numbers of males (50.6%) and females were included in the sample. Table 3.2 describes the baseline characteristics for the sample for determining the predictors for incidence of wheezing. The distributions of the two samples (in Tables 3.1 and 3.2) were very similar (data not shown).

3.3.2 Incidence of Asthma and Wheezing

Overall, the 4-year cumulative incidence of asthma and wheezing was 13.7% (1,001/8,499) and 17.6% (1,045/5919), respectively. Figure 3.1 presents the Kaplan-Meier estimates for the cumulative incidence of asthma and wheeze for some of the baseline factors. The cumulative incidence of asthma was consistently greater for children with histories of early wheeze and for the male sex (Figures 3.1 and 3.2). Children with histories of parental atopy had significantly greater cumulative incidence of asthma (Figure 3.3; $p<0.001$) and wheeze (Figure 3.4; $p<0.001$), compared to those without histories of atopy.

3.3.3 Risk Factors for Asthma and Wheezing

As shown in Table 3.1, a higher incidence of physician-diagnosed asthma occurred in the preschool years for children with a history of early wheezing as infants and as toddlers (HR: 2.34; 95% CI: 2.12-2.71). This association remained significant after adjusting for other potential confounders (HR: 2.23; 95% CI: 2.03-2.65). The following variables were associated with a significant reduction in physician-diagnosed preschool asthma: breastfeeding more than 3 months (HR: 0.82; 95% CI: 0.69-0.97); having 2 or more sibling at birth, (HR: 0.79; 95% CI: 0.64-0.97); having nose or throat infection often in childhood (HR: 0.79; 95% CI: 0.67-0.93); daycare attendance (HR: 0.85; 95% CI: 0.74-0.98); and dwelling in rural non-CMA centers (HR: 0.81; 95% CI: 0.69-0.95). Other factors retained in the optimal final model that were significant risk factors for incidence of preschool asthma were: male sex, geographic regions of dwelling, low birth weight, a child's history of allergy, maternal smoking during pregnancy, single parent household, parental atopy, and SES.

In multivariate modeling, factors associated with the incidence of wheeze were: male sex, geographic region, maternal age, history of nose or throat infection early in childhood, maternal use of prescription medication, single parent household, parental atopy, crowding at home, and breastfeeding (Table 3.2).

Interactions between some of the factors retained in each final model were also tested. Parental history of atopy had a significant interaction with early wheezing (p=0.014) and with breastfeeding (p=0.006) for predicting the incidence asthma. Nevertheless, the observed direction of these effects, after modification by the differences in history of parental atopy, did not change; an indication that the etiological effect of wheezing and breastfeeding on the incidence of asthma is not affected by the presence or absence of parental atopy.

3.4 Discussion

3.4.1 Comparison of Risk Factors for Asthma and Wheeze

This longitudinal study suggests that early childhood factors are associated with the development of asthma and wheezing at preschool age. Among the numerous factors examined at baseline, male sex, and maternal use of medication in pregnancy, single parent households, and maternal asthma were identified as significant risk factors for the development of both asthma and wheeze by preschool age. Significant factors that predicted the incidence of asthma, but not wheezing, were low birth weight, history of allergy, maternal smoking, very low socio-economic status, and dwelling in rural non-CMA. Breastfeeding and having a history of nose or throat infection early in childhood significantly reduced the risk for asthma but increased the risk for wheezing at preschool age. Although having two or more sibling at birth, and daycare attendance, did not predict the onset of wheezing in preschool years, both were associated with lower risks for the incidence of asthma. Younger maternal age and household crowding were not significantly associated with the development of asthma by school age, however, the former was a risk factor and the latter a protective factor for wheezing in preschool years.

3.4.2 Evidence of Risk Factors from Other Studies

To date, few population-based, longitudinal studies have been carried out among preschoolers to assess early-life factors for developing asthma and wheeze, or to examine the differential effects of risk factors for the onset of these conditions. Several studies have indicated that immunologic childhood markers are the strongest predisposing factors for asthma.[25,41-43] Many studies have also shown that the development of asthma and wheezing at this age is associated with family composition,[15,30] environmental tobacco smoke,[25,44] low family income or socio-economic class,[22,24,45] crowding,[46] sensitivity to allergen exposure,[47-50] daycare attendance,[30,51] hereditary factors,[21,29] residence on farm,[14,16,17,27,31] and male sex.[21] Most of these findings, however, were obtained from cross-sectional studies conducted mainly to understand the association and generate hypothesis. Consequently, the results from the current population-based, longitudinal study strengthen the etiological significance for these factors in the development of early childhood asthma and wheeze. The different predictors observed for the development of these conditions suggest that a different etiology may be underlining the development of asthma and wheeze early in childhood.

3.4.3 Impact of Early Wheezing on the Development of Asthma

In the current study, 20.3% (402/1981) of the children who had wheezing at baseline, before 2 years of age, went on to develop asthma (physician-diagnosed) in preschool (2 to 5 years of age), compared to 9.19% (599/6518) of the children who had no history of wheezing at baseline. In the multivariate analysis, early wheezing was identified as an independent risk factor for incidence of preschool asthma, and was associated with more than two times increased risk for developing asthma at preschool age. Recently, the role of wheezing in early life and the development of asthma later in life have been investigated in several studies.[10,52,53] Although asthma remains primarily a wheezing disease, not all children who wheeze continue to develop asthma at a later age. For this reason, the benefit of early therapy for wheeze among younger children, especially those who are under three years of age, is not clear. In any case, conclusions from a recent study indicate that early wheezers who may gain the most from early intervention, were those with obstructive and/or hyper-responsiveness lungs airway, or have the presence of atopy.[54] A clear link between early wheezing in infants and toddlers and the later onset of asthma has significant clinical implications for practitioners.

3.4.4 Support for the Hygiene Hypothesis

The findings from this study are in line with a review of previous findings related to the hygiene hypothesis from cross-sectional studies.[55] In particular, it was found that environmental factors that increase the likelihood for early infection in childhood such as daycare attendance, having more than one older sibling at birth, and not dwelling in urban centers have reduced risk for developing asthma. The 'hygiene hypothesis' advocates that early environmental exposures occurring in infants and toddlers has a significant potential to offset the Th1cell and Th2 cell imbalance in newborns and to prevent the early development of asthma among children.[56,57] The apparent inverse relationship between early-life factors in this study and the subsequent development of asthma supports the hypothesis. The only recent longitudinal study to assess the impact of the farming environment found an inverse relationship for the development of asthma.[18] In particular, when the rural environment is differentiated into farming and non-farming types, a strong reduced risk is seen for asthma being associated with the farming environment. This observation suggests that early exposure to infections from microorganisms and bacterial derivatives associated with livestock activities in farms, daycare settings, and older siblings at home may be associated with the lower incidence of asthma that is observed among the children dwelling in the farm settings. While the inverse relationship for daycare attendance appears to be conflicting in the literature, as some studies have found it to be a risk factor for asthma,[51,58] the inconsistent findings may be explained by daycare attendance that occurs at various ages during early life.

In the current study, breast feeding was a risk factor for incident wheezing, though it was a protective factor for the incidence of asthma. While breastfeeding has been shown to reduce the risk of atopy and asthma,[59,60] the evidence is conflicting. Some recent studies have demonstrated that breast feeding increases the risk for asthma and atopy.[61,62] Wright *et al.* demonstrated the paradoxical relationship between total serum IgE level in childhood and breastfeeding, that depended on maternal atopy, as determined by IgE level.[63] In the context of the 'hygiene hypothesis,' breastfeeding may enhance the early maturation of the immune system and prevent early infection[64] to reverse the potential gain that might be achieved from exposure to environmental factors that thwart the development of asthma.

3.4.5 Strengths and Limitations of this Study

The period effect (due to different times at which outcomes were assessed) and cohort effect (due to subjects not being introduced in the same year) can both influence the results of this longitudinal study. These factors were included in the models as confounding factors,[65] and an indicator variable was thus, introduced in each Cox's regression analysis to adjust for potential baseline differences between the two panels introduced at different time points. The AIC-optimal predictive factors obtained for both asthma and wheeze did not differ when the analysis was performed separately in each panel (data not shown) and the results were similar to those presented from the combined sample in Tables 3.1 and 3.2. When baseline characteristics of subjects, with complete follow-up during the study period, were compared with the subjects who were unavailable for follow-up or analysis, no systematic differences were found between the samples (data not shown). In addition, since physician diagnoses of asthma and wheeze were not confirmed by physicians or chart review, the outcome may be subject to some recall bias that could underestimate the true proportion of asthma in the population. Finally, we acknowledge that, treating infant and toddler wheezing as a risk factor for developing asthma at preschool age is not without controversy; as histories for wheezing is used in the diagnoses of asthma. However, in the analysis conducted for both incidence of asthma and wheezing, all children with history of physician-diagnosed asthma reported at baseline were excluded from study sample.

3.5 Conclusions

Early wheezing during the first year of life increased the risk for incidence of asthma, independent of other risk factors. Differences between the risk factors for incidence of asthma and wheeze emphasize the diagnostic and etiological differences of these conditions early in childhood. Although early environmental exposures are associated with incidence of asthma and wheeze, hereditary factors cannot be ignored. To develop effective prevention strategies for the development of asthma and wheeze in early childhood, mechanisms by which genetic and environmental factors interact and result in protective or risk factors for the development of asthma and wheeze need to be determined from future longitudinal studies.

3.6 Tables

Table 3.1 Early-life predictors of incidence of "physician-diagnosed asthma" at preschool age

Selected Characteristics	Study sample N*=8,499 (% of N)	Bivariate (unadjusted) analysis HR (95% CI)	Multivariable (adjusted) analysis HR (95% CI)
Panel 1 (1996 to 2001)	2,594 (50.7)		
Panel 2 (1998 to 2006)**	5,905 (49.3)	--	--
Early wheezing < age 2	1,981 (19.5)	2.34 (2.12-2.71)	2.23 (2.03-2.65)
Male sex (reference is females)	4,180 (50.6)	1.32 (1.18-1.49)	1.29 (1.14-1.46)
Geographic regions			
Atlantic	1,984 (6.5)	1.43 (1.09-1.87)	1.31 (0.98-1.73)
Quebec	1,541 (23.3)	1.57 (1.29-1.90)	1.58 (1.28-1.94)
Ontario	2,170 (39.2)	1.52 (1.27-1.82)	1.48 (1.22-1.79)
West (B.C)	738 (13.0)	0.90 (0.70-1.16)	0.97 (0.74-1.27)
Parries (reference)	2,066 (18.2)	1.00	1.00
Maternal age, yrs			
<20 yrs	285 (2.8)	1.38 (0.99-1.91)	--
20-25	1,872 (21.0)	1.38 (1.18-1.61)	--
26-30	2,981 (35.1)	1.25 (1.09-1.43)	--
>31 yrs (reference)	3,312 (41.2)	1.00	
Prenatal problems (yes/no)	2,389 (31.8)	1.20 (1.06-1.36)	--
Cesarean delivery (yes/no)	1,634 (18.2)	1.17 (1.01-1.35)	--
Low Birth weight (<2500g)	501 (6.1)	1.83 (1.51-2.23)	1.71 (1.39-2.10)
Ever breastfed <age 2			
Never	1,844 (20.3)	1.00	1.00
≤ 3 months	1,908 (22.6)	0.79 (0.66-0.94)	0.84 (0.70-1.00)
More than 3 months	4,548 (57.2)	0.71 (0.61-0.82)	0.82 (0.69-0.97)
Number of older siblings at birth			
None (reference)	3,729 (42.6)	1.00	1.00
1	3,421 (43.6)	0.95 (0.84-1.08)	1.05 (0.92-1.21)
≥2	1,349 (13.8)	0.81 (0.69-0.99)	0.79 (0.64-0.97)
Childhood allergy <age 2 (yes/no)	524 (5.8)	1.51 (1.23-1.85)	1.46 (1.18-1.81)
Ever had nose or throat infection < age 2 (yes/no)	1425 (16.0)	0.98 (0.84-1.15)	0.79 (0.67-0.93)
Ever attend daycare < age 2 (yes/no)	3,704 (39.1)	0.93 (0.93-1.05)	0.85 (0.74-0.98)
Either parent smoke (yes/no)	3,429 (39.8)	1.22 (1.09-1.37)	--
Maternal smoking			
None (reference)	6,302 (81.1)	1.00	1.00
1-5	633 (7.7)	1.29 (1.04-1.59)	1.16 (0.92-1.45)
> 5 cigarette/ day	924 (11.1)	1.34 (1.13-1.60)	1.29 (1.07-1.57)
Maternal use of prescription medication	2,119 (26.4)	1.46 (1.28-1.66)	1.32 (1.16-1.51)
Single parent household (yes/no)	829 (10.3)	1.52 (1.29-1.79)	1.43 (1.17-1.76)
Parental atopy (yes/no)	494 (6.1)	2.27 (1.88-2.76)	1.39 (1.22-1.59)
Household socio-economic status			
Very low (<-1.0)	963 (11.7)	1.37 (1.05-1.79)	1.35 (1.01-1.82)
Low (-1.0 to 0)	3,914 (43.5)	1.33 (1.05-1.67)	1.33 (0.98-1.78)
High (0 to 1.0)	2,887 (35.8)	1.15 (0.90-1.46)	0.98 (0.68-1.43)
Very high (>1.0)	735 (8.9)	1.00	1.00
Crowding (Person/bedroom<1.5)	410 (6.4)	0.83 (0.64-1.08)	--
Rural non CMA centers	2602 (20.3)	0.82(0.71-0.96)	0.81 (0.69-0.95)

* All baseline characteristics were assessed before subject were 2 years of age

*Sample comprise children with no prior history of physician-asthma at baseline

**Weights were provided by Statistics Canada to reflect the actual size of the target population.

Table 3.2 Early-life predictors of incidence of wheeze at preschool age

Selected Characteristics	Study sample N*=5919 (% of N)	Bivariate results HR (95% CI)	Multivariable results HR (95% CI)
Panel 1 (1996 to 2001)	1,889 (51.8)		
Panel 2 (1998 to 2006)**	4,030 (48.2)	--	--
Male sex (reference is females)	2,762 (48.5)	1.09 (0.97-1.23)	1.22 (1.08-1.40)
Geographic regions			
Atlantic	1,295 (6.0)	1.54 (1.16-2.03)	1.49 (1.11-1.99)
Quebec	1,061 (23.0)	1.64 (1.35-2.01)	1.61 (1.30-1.99)
Ontario	1,535 (38.1)	1.42 (1.18-1.72)	1.38 (1.14-1.68)
West (B.C)	577 (14.4)	0.99 (0.78-1.27)	0.91 (0.69-1.17)
Parries (reference)	1,451 (18.5)	1.00	1.00
Maternal age, yrs			
<20 yrs	175 (2.5)	1.72 (1.24-2.38)	1.46 (1.00-2.11)
20-25	1,198 (19.4)	1.27 (1.08-1.50)	1.13 (0.94-1.35)
26-30	2,097 (35.1)	1.20 (1.05-1.38)	1.14 (0.98-1.32)
>31 yrs (reference)	2,417 (43.1)	1.00	1.00
Prenatal problems (yes/no)	1,579 (30.8)	1.51 (1.32-1.72)	
Cesarean delivery (yes/no)	1,111 (17.7)	0.98 (0.84-1.15)	
Low Birth weight (<2500g)	311 (5.2)	0.81 (0.60-1.10)	
Ever breastfed < age 2			
Never	1,194 (18.6)	1.00	1.00
≤ 3 months	1,284 (22.2)	1.45 (1.20-1.75)	1.59 (1.29-1.94)
More than 3 months	3,309 (59.2)	1.00 (0.84-1.89)	1.10 (0.91-1.33)
Number of older siblings at birth			
None (reference)	2,587 (41.9)	1.00	
1	2,409 (44.4)	0.93 (0.82-1.06)	
≥2	923 (13.6)	0.76 (0.63-0.93)	
Childhood allergy < age 2 (yes/no)	296 (5.0)	0.79 (0.59-1.07)	
Ever had nose or throat infection < age 2 (yes/no)	828 (13.7)	1.02 (0.86-1.21)	0.95 (0.79-1.15)
Ever attend daycare < age 2 (yes/no)	2,489 (37.2)	0.98 (0.87-1.11)	
Either parent smoke (yes/no)	2,226 (37.1)	1.05 (0.92-1.19)	
Maternal smoking			
None (reference)	4,509 (83.5)	1.00	
1-5	392 (6.7)	0.98 (0.76-1.27)	
> 5 cigarette/ day	551 (10.0)	1.04 (0.84-1.28)	
Maternal use of prescription medication	1,366 (24.4)	1.25 (1.09-1.44)	1.18 (1.02-1.36)
Single parent household (yes/no)	491 (9.0)	1.32 (1.09-1.59)	1.20 (1.01-1.42)
Parental atopy (yes/no)	1,564 (25.3)	1.35(1.18-1.54)	1.44 (1.26-1.65)
Household socio-economic status			
Very low (<-1.0)	616 (11.6)	1.12 (0.86-1.45)	
Low (-1.0 to 0)	2,652 (42.0)	1.06 (0.85-1.32)	
High (0 to 1.0)	2,089 (36.9)	1.08 (0.86-1.35)	
Very high (>1.0)	562 (9.5)	1.00	
Crowding (Person/bedroom<1.5)	294 (6.8)	0.75 (0.57-0.98)	0.77 (0.61-0.96)
Rural non CMA centers	1,774 (19.9)	1.06 (0.92-1.23)	

*Sample comprise children with no prior history of physician-diagnosed asthma or wheezing at baseline

3.7 Figures

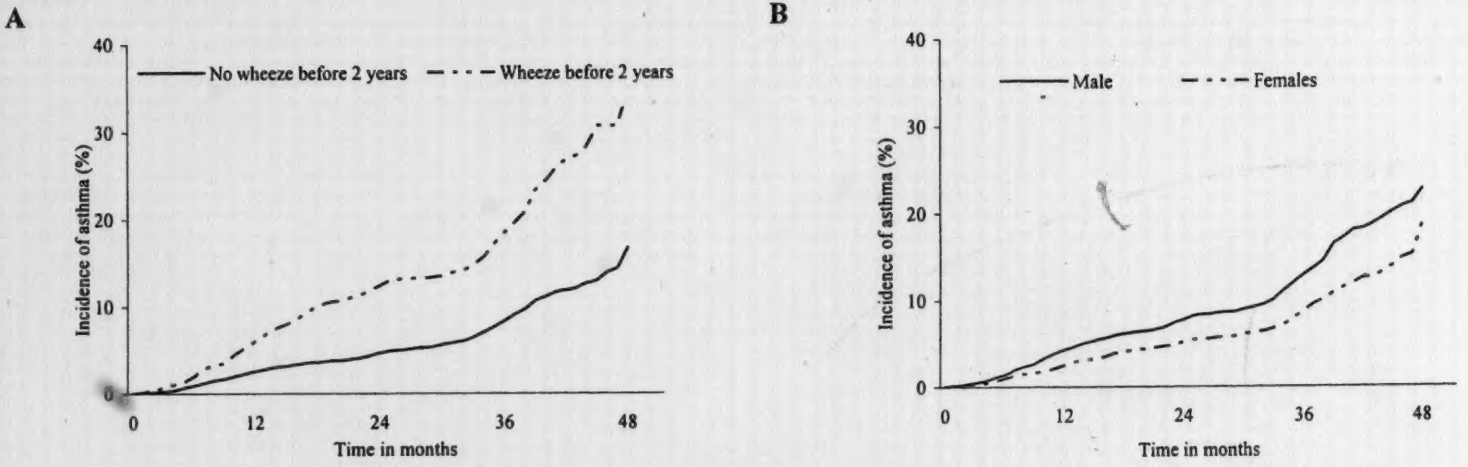

Figure 3.1 Survival graphs for the four-year (48 months) cumulative incidence of outcomes in preschool years (from age 2-5 years old): [(A) Asthma by of wheezing status, (B) asthma by sex at baseline]

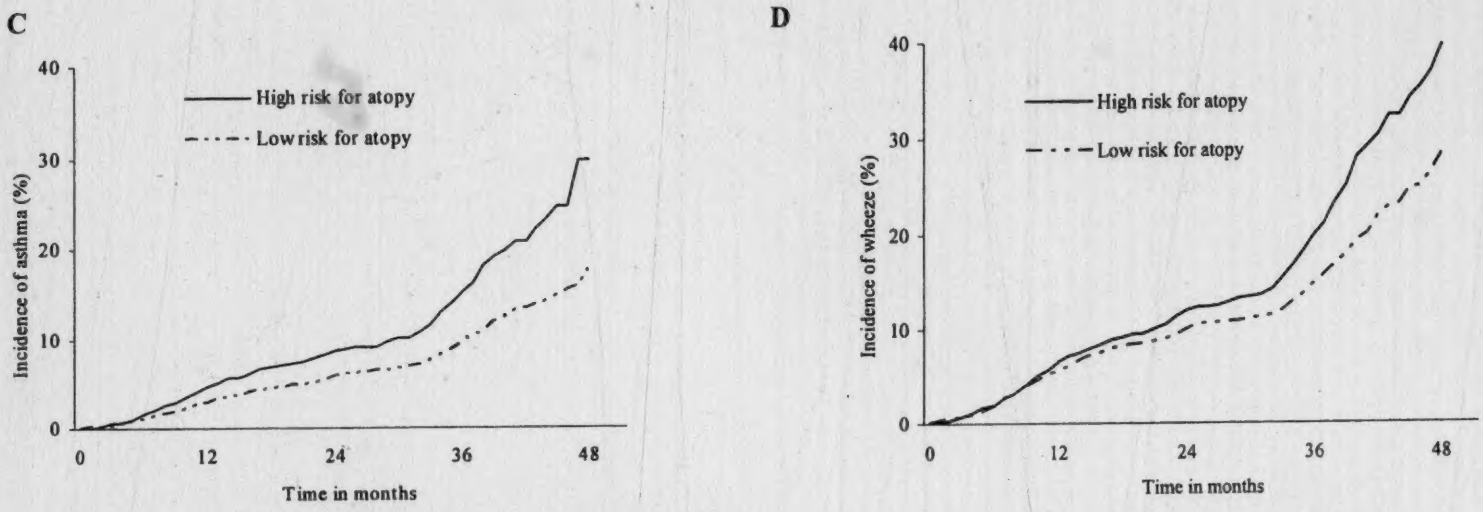

Figure 3.2 Survival graphs for the four-year (48 months) cumulative incidence of outcomes in preschool years (from age 2-5 years old): [(C) asthma by histories of parental atopy, and (D) wheezing by histories of parental atopy (presence of asthma or allergy) at baseline]

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Chapter 4

Predictors for wheezing phenotypes in the first decade of life[*]

4.1 Introduction

The diagnosis of childhood asthma can be complicated by different patterns of wheezing occurrences among children as they progress towards adolescence. Although wheezing is very common in early life, especially among infants and toddlers (<3 years of age), some children go into remission, while others may have recurrent episodes that persist into adolescence. Furthermore, some children who have never experienced wheezing during early childhood may suddenly develop the disease at their transition into adolescence, this is especially true for girls. These wheezing phenotypes present diagnostic, prognostic, and management challenges for physicians who treat children.[1, 2]

Some of the distinct patterns of wheezing that occur in young children are: transient early wheeze, late-onset wheeze, persistent wheeze, and non-wheezing phenotypes.[3,4] Measurements of lung function among these phenotypes has been recently investigated.[5-11] Although transient early wheezing was not associated with reduced lung function,[9,10] persistent wheezing was associated with lower lung function and development of asthma in later life.[6,8,10] In a New Zealand study, subjects who were identified as persistent wheezers in childhood had reduced lung function in adulthood.[11] These studies support the idea that development of wheezing may have different etiological origins, and that an understanding of the factors associated with each of these phenotypes might help to guide early interventions intended to prevent persistent wheeze and the development of asthma later in life.

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Although the prognoses with reference to lung function and clinical outcomes among these phenotypic classifications have been well documented,[6,11] epidemiological risk factors for these conditions have not been extensively studied. Recently, birth cohort studies have been conducted to determine the role of early-life characteristics and factors during pregnancy as predictors of these phenotypic sequences for both atopic diseases[4] and wheezing illness[12-14] among children. The current study reports early-life factors which are predictors for these phenotypes among Canadian children. The study is based on samples of infants and toddlers (ages < 24 months) drawn from the first panel (1994/95) of the NLSCY, and followed-up at subsequent cycles conducted between 1996 and 2003.

4.2 Material and Methods

4.2.1 Study Population

A detailed description of the NLSCY data has been presented elsewhere[15] (see Appendix A). The study population was comprised of longitudinal surveys conducted two years apart at five time points as follows: Cycle 1 (1994/95, n=16,903); Cycle 2 (1996/97, n=15,468); Cycle 3 (1998/99, n=14,997); Cycle 4 (2000/01, n=13,310); and Cycle 5 (2002/03, n=12,523). The main outcome considered in this study is wheezing phenotypes, which is defined using the sequence of wheeze occurrences that was reported for each child in the five cycles of the NLSCY.

4.2.2 Study Sample

The sample for analysis in this study included 2,711 (70%) of the initial 3,950 infants and toddlers (ages < 24 months) who participated in the longitudinal cohort at Cycle 1. These children were chosen because they had complete information on all selected baseline variables, and the person most knowledgeable provided responses to the current wheeze questionnaire at every cycle during the follow-up. Also, the study sample was restricted to infants and toddlers due to lack of prenatal and perinatal information for older children with age greater than 3 years old at baseline.

4.2.3 Definition of Wheeze Phenotypes

Each subject was classified into one of the five mutually exclusive phenotypes (Table 4.1) based on the presence or absence of wheezing illness during preschool years (0-5 years of age), and during primary schooling years (6 to 9 years of age). Children with at least one reported wheezing episode during their preschool years and no reported wheezing during primary school years were classified as preschool wheezers. Children who had no reported wheezing during preschool years but reported at least one episode during their primary school years were classified as primary school wheezers. Children who intermittently reported at least one wheezing episode during both periods of preschool and primary school years were classified as intermittent wheezers. Children with two consecutive reports of wheeze during preschool years and primary school years were classified as persistent wheezers. Children who did not report wheeze during both preschool and primary school years were classified as non-wheezers (used as the reference population in the analysis). The definitions used in this study are comparable with other definitions of wheeze phenotypes that were used previously in other studies.[8,16]

4.3.4 Selection of Predictor Variables

Several independent factors that were related to a child's personal characteristics during prenatal, perinatal, and early childhood periods were considered in the study. Baseline demographic variables and birth characteristics, such as low birth weight (<2500g), prematurity (<37 weeks of gestational age), medical conditions at birth, sex, history of breastfeeding, daycare attendance, household socio-economic status, parental history of asthma, passive cigarette exposure due to parental smoking, home environment, housing condition, neighborhood factors, and geographic regions of Canada (Atlantic, Quebec, Ontario, Prairies, and British Columbia) were included in the analysis. Further details of these factors can be found in the Appendix or from detail materials published elsewhere.[17,18] Each household was classified according to location in an urban or Central Metropolitan Area (CMA). Socio-economic status (SES) was derived by Statistics Canada based on annual family income of each household, parental education, and occupational status of both parents. The SES variable was divided into quartiles for the analysis. Body mass index (BMI) was derived as weight (kg) per squared height (m^2). It was dichotomized at the 85th percentile in the analysis to provide an indicator of overweight children. A crowding index for each household was determined by dividing the number of reported occupants in the home by the number of living rooms and bedrooms available at the baseline; it was dichotomized at 1.5 people per room. All baseline characteristics selected for this study were identified from the literature[7,9,12-14,19-27] as potential predictors associated with the development of wheezing conditions and asthma in childhood.

4.2.5 Statistical Analysis

The sampling frame used in the NLSCY to select children from the whole population of children dwelling in Canada was based on a complex multistage sampling method. Therefore, Statistics Canada provided longitudinal weights for use in all analyses, to adjust for the probability of selection, non-responses, and post-stratification. All initial analyses in this study were performed in SAS (SAS institute, Inc. Cary, NC)[28] with normalized longitudinal weights. Descriptive statistics were presented for the distribution of baseline characteristics and compared among the phenotypes. Differences were tested using chi-square tests for comparison of proportions between multiple groups. Fisher exact tests were also used for cells with expected counts of less than five.

In the analysis, the first polytomous regression methods[29,30] in the SAS LOGISTIC procedure[31] were used to test the bivariate association for all selected baseline factors with the four wheezing phenotypes. Variables identified as potential predictors of wheezing phenotypes were selected at $p<0.20$ significance testing. Next, a multivariable analysis was performed using a stepwise method to reduce the list of potential predictors to include only those with significant testing at $p<0.10$. All variables remaining in the reduced model were further analyzed using a modified stepwise logistic regression[32,33] separately for each phenotype. Although the polytomous logistic procedure could assess the predictors jointly for phenotypes, since the intention was to facilitate identification of different sets of predictors for each condition, the final analysis was performed using four separate logistic regressions for each phenotype. The non-wheezers were used as the reference population for each analysis of the other four phenotypes. The modified selection approach is considered optimal as long as the number of subjects in the reference population is not too small.[32] The variables remaining in each final model for the four phenotypes included a pool of best subset predictors selected from both AIC (Akaike information criteria) and SIC (Schwarz information criteria) – optimal models of the stepwise sequence.[32-35]

Finally, to adjust for the design effect of the NLSCY and to obtain a robust estimate, the SUDAAN (Research Triangle Park, NC, USA)[36] calculable procedure in the SAS was used to obtain the odds ratios (OR) and the 95% confidence interval (95% CI), based on the 1000 bootstrap weight, provided by Statistics Canada for subjects with complete information at Cycle 5. The supplementary analysis was performed using a method of retention analysis for longitudinal data[37] to test the impact of non-respondent and drop-outs, including cases that were excluded from the study due to missing responses at the baseline.

4.3 Results

4.3.1 Wheeze Prevalence in the Longitudinal Cohort

Table 4.1 presents the distribution of the study sample by wheezing phenotypes. Of 2,711 children, 25.4% of the cases were preschool wheezers, 8.5% were primary school wheezers, 6.7% were intermittent wheezers, 9.9% were persistent wheezers, and 49.5% were non-wheezers. From Figure 4.1, the cumulative incidences of physician-diagnosed asthma, occurring within the follow-up period, is highest among the persistent wheezers (83.9%), followed by intermittent wheezers (52.8 %), primary-school wheezers (27.6%), preschool wheezers (28.1%), and non-wheezers (5.6%). For the majority of children, wheezing in early preschool years was benign and did not persist into primary school; i.e., of the 1,138 children who wheezed in preschool age, over 60% did not continue to wheeze at primary school.

4.3.2 Baseline Characteristics by Wheezing Phenotype

Table 4.2 presents the distribution of baseline characteristics of the study cohort by wheezing phenotypes. The persistent wheezers had a greater proportion of males (62.3%), children with respiratory infection (15.3%), history of prenatal complications (39.5%), history of allergy (38.2%), reported low health status at birth (17.1%), parental history of asthma (31.8%), and dwelling in homes needing major repairs (26.7%). The proportion of breast feeding (64.4%) was highest among the intermittent group, and daycare attendance (42.6%) was highest among preschool wheezers. No reports were found of respiratory infection at baseline among primary school wheezers, and the proportion of reported low health status at birth (4%), and personal history of allergy (18%) were lowest in this group, compared to the other phenotypes.

4.3.3 Factors Associated with Preschool Wheeze

The bivariate and multivariate factors associated with wheeze phenotypes are shown in Tables 4.3 and 4.4. The following variables have significant bivariate association with preschool wheezing: respiratory infection, history of prenatal complication, breastfeeding, prematurity (<37 weeks of gestational age), personal history of allergy, low health status rated at birth, daycare attendance, history of parental asthma, history of parental smoking, and dwelling in crowded homes. The factors associated with preschool wheeze in the multivariable analysis (Table 4.4) include: respiratory infection (OR; 5.15; 95% CI: 2.57-10.33), breastfeeding (OR=1.54; 95% CI: 1.13-2.09), history of allergy (OR=2.25; 95% CI: 1.50-3.39), daycare attendance (OR=1.50; 95% CI: 1.11-2.03), parental asthma (OR=2.35; 95% CI: 1.49-3.71), parental smoking (OR=1.53; 95% CI: 1.14-2.06), and crowding (OR=0.69; 95% CI: 0.50-0.94).

4.3.4 Factors Associated with Primary-School Wheeze

For primary school wheezers, low health status reported at birth demonstrated a statistically significant association in the bivariate testing. Other significant factors showing bivariate association were parental asthma and crowding at homes. Children from the Atlantic and British Columbia regions were more likely to experience wheezing during primary school ages, compared to the children from the Prairies region. In the multivariate analysis, significant independent factors associated with primary school wheeze were: daycare attendance (OR=0.36; 95% CI: 0.14-0.94), parental asthma (OR=2.38; 95% CI: 1.23-4.61) and crowding (OR=0.44; 95% CI: 0.26-0.74).

4.3.5 Factors Associated with Intermittent Wheeze

For intermittent wheezers, significant bivariate associations were found for history of respiratory infection, low birth weight, breast-feeding, prematurity (<37 weeks of gestational age), personal history of allergy. Independent predictors were respiratory infection (OR=4.76; 95% CI: 1.83-12.37), breast feeding (OR=1.94; 95% CI 1.22-3.09), prematurity (OR=2.37; 95% CI: 1.18-4.76) and history of allergy (OR=2.42; 95% CI: 1.40-4.17).

4.3.6 Factors Associated with Persistent Wheeze

In the bivariate analysis, the factors significantly associated with persistent wheeze were: male sex, respiratory infection, presence of prenatal complication, personal history of allergy, low health status reported at birth, and history of parental asthma. In the bivariate analysis, subjects from the Atlantic and Quebec regions were more likely to experience persistent wheeze when compared to children from the Prairies region. In the multivariate analysis, independent factors associated with persistent wheeze were: male sex (OR=1.89; 95% CI: 1.17-3.05), history of respiratory infection (OR=8.44; 95% CI: 3.05-23.33), history of allergy (OR=4.84; 95% CI: 3.03-7.74), health status at birth (OR=2.18; 95% CI: 1.10-4.33), history of parental asthma (OR=7.21; 95% CI: 3.99-13.06) and dwelling needing repairs (OR=1.74; 95% CI: 1.05-2.87).

4.3.7 Retention Analysis

Since drop-outs and non-respondents may have implications for the interpretation of results from this longitudinal study, the retention rates were assessed for the infant and toddler cohort to examine baseline factors associated with retention. Most respondents (2,798/3,950) provided a complete sequence for use in this analysis. The response rates were 92% at Cycle 2, 89% at Cycle 3, 79.7% at Cycle 4, and 77% at Cycle 5.

Approximately 31% (1,239/3,950) of the subjects who were excluded from the final analysis, either due to missing baseline data or incomplete information provided during the follow-up period, were compared to the sample included (2,711) in the analysis (Table 4.5). For the variables that showed significance association with wheeze phenotype in the final multivariate analysis, respiratory infection, male sex, personal history of allergy, and daycare attendance at baseline were significantly more prevalent among subjects who were included in the analysis, compared to those who were excluded, in comparison to the overall sample at baseline. Retention analysis indicated that crowding at home and socio-economic status were the significant factors that were correlated with the propensity for inclusion.

4.4 Discussion

4.4.1 Summary of Findings

This large, longitudinal study of children across Canada identified different sets of prenatal, postnatal, and early-life factors that occur before the age of two years, that were strongly associated with various well-defined wheezing phenotypes in the first decade of life. Overall, while the final models were unique, some overlap was seen between the predictors of different phenotypes. The principal risk factors associated with preschool wheeze were: breast-feeding, personal allergy, daycare attendance, respiratory infection, parental history of asthma, and parental smoking. In longitudinal studies conducted in the last decade, factors emerging as significant for transient wheeze were predominantly the exposures that occur in early-life.[9,12,14,24] These factors have been largely identified to be associated with small airways and with the risk of lower respiratory virus infection (LRI), due to living with older siblings or attending daycare.[9,38] Maternal and passive smoking has been clearly shown to be associated with early wheezing.[25] The role of breast-feeding in early wheezing, however, is not clearly understood. While this study demonstrates that breastfeeding is a potential risk factor for both transient and intermittent wheezing, some studies have found it to be protective for transient or early wheezing in childhood.[13,14,24,26] These contradictory findings might be explained by the paradoxical relationship between breast-feeding and immunoglobin E (IgE) levels in children.[27] Although children who wheeze early in life are more likely to wheeze later, transient early wheeze was not associated with an increased risk of methacholine hyper-responsiveness or atopy.[9,38,39]

Approximately one in every six children in this study demonstrated wheezing only in their primary school years. The factors associated with this late-onset wheezing phenotype were: daycare attendance, parental asthma, and crowding. Despite the association with parental asthma, a child’s history of allergy at baseline was not a significant predictor of wheezing during primary school. Daycare attendance was positively associated with preschool wheezing but negatively associated with primary school wheezing. This finding is consistent with the results from other studies to determine risk factors for wheezing phynotypes.[13,14] Daycare attendance in the first year of life increased the risk of illnesses of the upper and lower respiratory tract for children with a familial history of atopy.[40] As a possible explanation for this, for infants who are predisposed to a risk of atopy, acquired infection from increased exposure to daycare facilities early in life may affect the Th1:Th2 cell relationship which may, in turn, reduce the risk for onset of wheezing at school age.[13,14,41,42,42]

In this study, crowding at home was protective against both preschool and primary school wheeze, but not for other phenotypes. This finding suggests that children living in crowded homes might be at increased risk for infections from older siblings and other members in the household. Significant predictors of intermittent wheezing found in this study were: presence of allergy, respiratory infection early in childhood, breast-feeding, and pre-term birth. Evidence suggests that children who experience this intermittent wheezing phenotype are more likely to receive a diagnosis of asthma in their preschool years.[9] This is consistent with Figure 1, which shows a sharp increase in physician-diagnosed asthma during primary school age among the intermittent wheezers.

In this study, the risk factors associated with persistent wheeze were mainly: parental asthma, child allergy, and other prenatal and prenatal factors. A stronger positive association was seen between persistent wheezing and parental asthma and personal allergy, compared to the associations with preschool wheezing. In other studies, persistent wheeze was associated with increased responsiveness to methacholine, increased peak-flow variability, increased total IgE levels, increased prevalence of atopy determined by skin-prick tests, and significant impairment of lung function later in life.[9,38,39] Male sex was a significant risk for persistent wheezing but not for the other phenotypes. Some evidence suggests that persistent asthma-like symptoms are observed more often among males early in life, which then reverses to be observed more often among females by adolescence.[43] Finally, Figure 4.1 shows that persistent wheezing was associated with an increased rate of physician-diagnosed asthma, which reaches a peak by the end of the first decade of life.

4.4.2 Limitations of this Study

In this study, some limitations should be considered. First, no universally accepted definition exists for wheezing phenotypes among children. Hence, the results from this study cannot be directly compared to those of previous studies with similar objectives since different definitions may have been used.[5,10,12-14,24] Second, at each cycle, current wheeze was reported for the 12 months following the interview date. Therefore, parents of children who wheezed only within the first year after a survey was completed might not have reported the wheezing episode at a subsequent survey conducted two years after the earlier survey. Nevertheless, the use of current wheeze (wheeze within previous 12 months) minimizes the recall bias and increases the reliability of categorization used to define the wheezing phenotypes. Third, the results are based on self-reported outcomes; no attempt was made to confirm the diagnoses by physicians or to use chart review. While this is a common weakness of surveys, questionnaire data such as that employed in the NLSCY has been validated in population-based studies.

4.5 Summary and Conclusion

In summary, wheezing in the first decade of life occurred mainly in children's preschool years. As these wheezing children progress to primary school, recurrent episodes of wheezing decrease. Risk factors for each wheeze phenotype differ albeit some degree of overlap occurs. These variations suggest different pathogenesis for wheezing among children, and by extrapolation, these results have implications for the development of other lung diseases including asthma, among children. Parental and early childhood factors were important determinants of the phenotypes. To further elucidate the causal mechanism underlying each of these phenotypic sequences, longitudinal studies with time-dependent factors are required to explore how environmental factors that change over time might influence wheezing as children progress to young adulthood.

4.6 Tables

Table 4.1 Definition of wheezing phenotype within first decade of life for the NLSCY study cohort

		Wheeze episodes in preschool years (age ≤ 5 yrs)					Wheeze episodes in primary school years (age 6-9 years)		
Wheezing phenotypes	Sample[†] (n) (%)	None	One (1)	or Two (2)	or three (3)		None	One (1)	or Two (2)
Non wheezers	1342 (49.5)	√				and	√		
Preschool wheezers	690(25.4)		√	√	√	and	√		
Primary school wheezers	231(8.5)	√				and		√	√
Intermittent wheezers	181(6.7)		√			and		√	√
Persistent wheezers	267 (9.9)			√	√	and		√	√

The Canadian National Longitudinal Survey of Children and Youth (NLSCY) Cycles 1, 2, 3, 4, and 5, was conducted between 1994 and 2003. Follow-up was made for each subject between ages < 10 years inclusive.

[†] Sample includes 2711 infant and toddlers, with complete information at baseline and on wheezing outcome at each Cycle.

[√] Indicate number of reported wheeze or a potential pattern of subject response in preschool years or at primary school years.

Table 4.2 Distribution of selected baseline characteristics by wheeze phenotype

Baseline factors (At Cycle 1)	Overall[†] Sample	Wheezing phenotypes[‡]					p-value
		Non wheezers	Preschool wheezers	Primary school wheezers	Intermittent wheezers	Persistent wheezers	
	n=2711	n=1342	n=690	n=231	n=181	n=267	
Respiratory infection < age 2	5.41	1.94	9.22	---	7.86	15.29	<0.001
History of prenatal complications	27.29	23.40	29.84	28.61	27.52	39.54	<0.001
Sex , Male	49.82	47.35	49.96	48.03	51.73	62.32	0.001
Low Birth Weight (< 2500g)	5.86	4.63	7.00	5.03	11.42	6.56	0.004
Breast-feeding < age 2	53.68	49.37	61.60	50.28	64.39	52.94	<0.001
Prematurity (<37 wks)	9.67	7.77	12.14	8.20	18.10	9.37	0.002
Overweight kg/m^2 (>85 percentile)	13.66	14.11	13.52	11.42	10.46	15.78	0.736
Personal history of allergy < age 2	18.70	11.55	24.28	17.91	25.11	38.18	<0.001
Health status rated low at birth	10.73	9.13	14.48	3.63	9.33	17.10	<0.001
Maternal smoking in pregnancy	18.66	16.79	20.37	19.57	18.64	23.31	0.077
Daycare attendance < age 2	35.35	32.10	42.56	27.16	38.90	39.64	<0.001
Maternal age at birth(<25 yrs)	21.56	19.78	24.93	22.30	20.80	22.39	0.127
History of parental asthma	11.90	6.55	14.45	13.20	11.65	31.82	<0.001
History of parental smoking	50.14	46.30	54.49	52.77	57.76	52.05	0.001
Household SES							
Low (lower quartile)	20.92	20.92	20.39	23.37	17.46	22.17	0.647
Moderately low	24.08	22.55	20.59	29.57	36.08	27.72	<0.001
Average	24.81	24.60	27.38	18.16	26.88	24.33	0.075
High (Upper quartile)	30.19	31.93	31.64	28.90	19.58	25.78	0.006
Crowding (n>=1.5/bedroom)	33.68	38.12	27.95	22.82	30.49	36.52	<0.001
Dwelling need repairs	21.42	20.15	23.39	19.41	18.58	26.73	0.067
Residing in CMA/urban centers	68.44	68.41	66.51	67.84	72.51	71.14	0.346
Geographic regions							
Atlantic	8.04	7.00	8.13	8.81	11.15	10.51	0.151
Québec	24.89	22.21	29.54	21.47	24.95	30.39	0.001
Ontario	36.06	37.43	33.04	36.29	36.35	35.89	0.447
British Columbia	11.90	12.64	10.06	19.60	7.56	8.41	<0.001
Prairies	19.11	20.73	19.23	13.83	20.00	14.79	0.039

The Canadian NLSCY infants and toddler cohort (less than 2 years) at Cycle 1 (1994/95) and with complete information at Cycle 5 (2002/2003)

[*] Percentages are weighted using longitudinal weights for cohort followed from Cycle 1 to Cycle 5. Weights are normalized for the infant and toddler cohort.

[†] Percentages are with respect to total number of cases in the study sample (n=2711).

[‡] Percentages are with respect to number of cases in each wheeze phenotype.

Table 4.3 Bivariate odds ratio (OR) and 95% confidence interval (95% CI) for factors associated with wheezing phenotypes

	Wheezing phenotypes			
Baseline factors	Preschool wheezers OR (95% CI[†])	Primary school wheezers OR (95% CI[†])	Intermittent wheezers OR (95% CI[†])	Persistent wheezers OR (95% CI[†])
Respiratory infection < age 2	5.14 (2.29-11.54)	1.07 (0.22-5.28)	4.32 (1.53-12.21)*	9.14 (3.69-22.68)*
History of prenatal complications	1.39 (1.03-1.87)*	1.33 (0.80-2.15)	1.24 (0.75-2.06)	2.14 (1.41-3.24)*
Sex , Male	1.11 (0.84-1.47)	1.03 (0.67-1.58)	1.19 (0.75-1.89)	1.84 (1.21-2.79)*
Low Birth Weight (< 2500g)	1.55 (0.80-3.01)	1.09 (0.51-2.33)	2.65 (1.14-6.20)*	1.45 (0.64-3.24)
Breast-feeding < age 2	1.65 (1.24-2.19)*	1.04 (0.67-1.60)	1.85 (1.18-2.90)*	1.15 (0.76-1.75)
Prematurity (<37 wks)	1.64 (1.00-2.68)*	1.06 (0.44-2.56)	2.62 (1.35-5.09)*	1.23 (0.65-2.32)
Overweight kg/m^2 (>85 percentile)	0.95 (0.64-1.42)	0.78 (0.42-1.46)	0.71 (0.40-1.28)	1.14 (0.66-1.97)
Personal history of allergy < age 2	2.45 (1.67-3.60)*	1.67 (0.91-3.07)	2.57 (1.57-4.21)*	4.73 (3.06-7.30)*
Health status rated low at birth	1.68 (1.09-2.60)*	0.38 (0.15-0.93)*	1.02 (0.54-1.93)	2.05 (1.20-3.52)*
Maternal smoking in pregnancy	1.27 (0.89-1.81)	1.21 (0.70-2.09)	1.14 (0.67-1.92)	1.51 (0.89-2.55)
Daycare attendance < age 2	1.57 (1.18-2.08)*	0.79 (0.50-1.24)	1.35 (0.85-2.13)	1.39 (0.88-2.19)
Maternal age at birth(<25 yrs)	1.35 (0.98-1.85)	1.16 (0.72-1.87)	1.07 (0.58-1.95)	1.17 (0.76-1.80)
History of parental asthma	2.41 (1.55-3.73)*	2.17 (1.16-4.04)*	1.88 (0.97-3.64)	6.65 (4.01-11.03)*
History of parental smoking	1.39 (1.03-1.88)*	1.30 (0.83-2.02)	1.59 (0.98-2.56)	1.26 (0.83-1.90)
Household SES				
Low (lower quartile)	0.98 (0.67-1.46)	1.23 (0.68-2.25)	1.36 (0.70-2.66)	1.31 (0.73-2.36)
Moderately low	0.92 (0.62-1.36)	1.45 (0.78-2.70)	2.61 (1.35-5.06)*	1.52 (0.83-2.81)
Average	1.12 (0.77-1.63)	0.82 (0.42-1.58)	1.78 (0.91-3.50)	1.23 (0.70-2.14)
High (Upper quartile)	1.00	1.00	1.00	1.00
Crowding (n>=1.5/bedroom)	0.63 (0.47-0.85)*	0.48 (0.29-0.79)*	0.71 (0.41-1.25)	0.93(0.60-1.44)
Dwelling need repairs	1.21 (0.89-1.65)	0.95 (0.57-1.59)	0.90 (0.54-1.51)	1.45(0.92-2.28)
Residing in CMA/urban centers	0.92 (0.70-1.20)	0.97 (0.65-1.47)	1.22 (0.79-1.89)	1.14 (0.78-1.67)
Geographic regions				
Atlantic	1.25 (0.85-1.85)	1.89 (1.06-3.37)*	1.65 (0.88-3.11)	2.11 (1.20-3.69)*
Québec	1.43 (0.98-2.10)	1.45 (0.79-2.67)	1.16 (0.62-2.17)	1.91 (1.03-3.56)*
Ontario	0.95 (0.66-1.37)	1.45 (0.81-2.61)	1.01 (0.54-1.87)	1.34 (0.78-2.31)
British Columbia	0.86 (0.51-1.44)	2.32 (1.13-4.78)*	0.62 (0.24-1.60)	0.93 (0.42-2.09)
Prairies	1.00	1.00	1.00	1.00

*Factors showing significant for bivariate association with wheezing phenotype in the polytomous analysis

[†] For each confidence interval (CI), we adjusted for design effects using 1000 longitudinal bootstrap weights provided by Statistics Canada for NLSCY at Cycle 1.

Table 4.4 Multivariate odds ratio and 95% confidence interval for factors associated with wheezing phenotypes

Baseline factors	Wheezing phenotypes			
	Preschool wheezers OR (95% CI)	Primary school wheezers OR (95% CI)	Intermittent wheezers OR (95% CI)	Persistent wheezers OR (95% CI)
Respiratory infection < age 2	5.15 (2.57-10.33)		4.76 (1.83-12.37)	8.44 (3.05-23.33)
Sex , Male				1.89 (1.17-3.05)
Breast-feeding < age 2	1.54 (1.13-2.09)		1.94 (1.22-3.09)	
Prematurity (<37 wks)			2.37 (1.18-4.76)	
Personal history of allergy < age 2	2.25 (1.50-3.39)		2.42 (1.40-4.17)	4.84 (3.03-7.74)
Health status rated low at birth				2.18 (1.10-4.33)
Daycare attendance < age 2	1.50 (1.11-2.03)	0.36 (0.14-0.94)		
History of parental asthma	2.35 (1.49-3.71)	2.38 (1.23-4.61)		7.21(3.99-13.06)
History of parental smoking	1.53 (1.14-2.06)			
Crowding (n>=1.5/bedroom)	0.69 (0.50-0.94)	0.44 (0.26-0.74)		
Dwelling need repairs				1.74(1.05-2.87)

All analysis was performed with separate modified stepwise logistic regression for each phenotype and adjusted for geographic region.

[†] Confidence interval (CI), were obtained from using 1000 longitudinal bootstrap weights provided by Statistics Canada for NLSCY at Cycle 5 to adjust for design effects.

Table 4.5: Baseline characteristics of children included and excluded from analysis.

Sample characteristics at baseline	Distribution of baseline characteristic			Association parameters for inclusion	
	Overall	Included	Excluded		
	(N=3950)	(n=2711)	(n=1239)	OR	p-value†
Respiratory infection < age 2	4.70	5.41	3.16	1.75	0.039
History of prenatal complications	25.13	27.29	20.42	1.44	0.001
Sex , Male	51.20	49.82	54.21	0.84	0.104
Low Birth Weight (< 2500g)	6.01	5.86	6.35	0.92	0.718
Breast-feeding < age 2	53.39	53.68	52.75	1.04	0.705
Prematurity (<37 wks)	9.36	9.67	8.67	1.13	0.535
Overweight kg/m^2 (>85 percentile)	19.89(7.23)	19.73(7.02)	20.28(7.70)	0.99	0.201
Personal history of allergy < age 2	14.57	18.70	5.52	3.93	0.001
Health status rated low at birth	11.17	10.73	12.14	0.87	0.383
Maternal smoking in pregnancy	20.41	18.66	24.23	0.72	0.007
Daycare attendance < age 2	33.32	35.35	28.89	1.35	0.013
Maternal age at birth(<25 yrs)	24.22	21.56	30.05	0.64	0.001
History of parental asthma	10.45	11.90	7.30	1.72	0.004
History of parental smoking	49.18	50.14	47.08	1.13	0.265
Household SES‡	-0.08(0.78)	0.02(0.75)	-0.29(0.81)	1.70	<0.001*
Crowding (n>=1.5/bedroom)‡	1.42(0.47)	1.40(0.46)	1.50(0.52)	0.67	0.003*
Dwelling need repairs	21.24	21.42	20.42	1.03	0.810
Residing in CMA/urban centers	70.38	68.44	74.63	0.60	0.003
Geographic regions					
Atlantic	7.41	8.04	6.01	1.17	0.299
Québec	23.75	24.89	21.27	1.07	0.896
Ontario	38.29	36.06	43.17	0.73	0.023
Prairies	12.21	11.90	12.89	0.80	0.235
British Columbia	18.85	19.11	16.66	1.00	

‡Values are presented as means and standard deviation in parenthesis. These variables were analyses as continuous variables in the retention analysis. †Univariate p-value with propensity for inclusion in the study sample. *Significant factors remaining after adjustment in the multivariate retention model

4.7 Figures

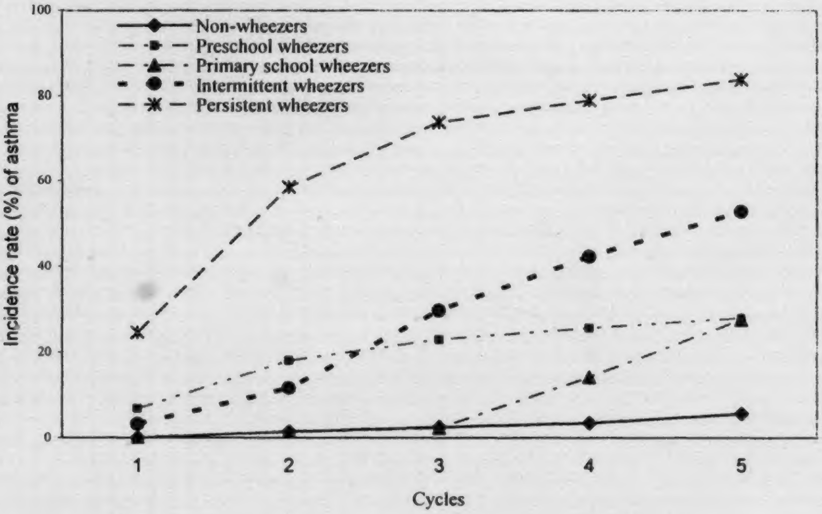

Figure 4.1 Cumulative incidence of physician-diagnosed asthma

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Chapter 5

Overall Summary, Discussion, and Conclusions

5.1 Overview

This thesis, primarily examined a longitudinal cohort to assess the role of prenatal and early-life factors occurring in infants and toddlers (<2 years of age) and the development of asthma and wheeze among Canadian children as they progress to adolescence. In particular, environmental exposures that have the potential to modify or prevent the development of these conditions early in life were investigated. This study determined the incidence of childhood asthma and wheezing and the risk factors associated with them, from data collected from a nationwide population-based longitudinal study conducted in Canada.

5.1.1 Main Contributions of the Thesis

The primary importance of this study is in providing longitudinal epidemiologic evidence to support the currently debated, basic tenet for the hygiene hypothesis and in applying advanced statistical techniques. In recent years, several cross-sectional studies have been conducted[1-16] most of which indicated that dwelling in a farming environment is associated with a lower prevalence of asthma. To date, however, no longitudinal study has been conducted to assess this conclusion. As a consequence, the study presented in Chapter 2 is the first of its kind that uses a longitudinal perspective to examine the association between dwelling in a farming environment and the development of asthma.

Also, innovative method such as bootstrapping and modified stepwise statistical techniques were used to obtain robust estimates and identify the optimal set of factors associated with development of asthma and wheezing in the NLSCY.

5.1.2 The Hygiene Hypothesis and Its Implications

The hygiene hypothesis has gained important support over the past few years because environmental exposures and traditional lifestyles, such as dwelling in a farming environment,[1-16] daycare attendance,[17-20] large family size,[17,20,21] and other factors were seen to be associated with a lower prevalence of atopic diseases including asthma. Until recently, the apparent inverse relationship between these factors and the subsequent development of asthma and atopy was based on epidemiological associations, though this finding currently has support from immunological grounds as well.

5.2 Summary of Results and Discussion

5.2.1 Effect of Dwelling in a Farm Environment

In a two-year, follow-up study, the cumulative incidence of asthma among children living in farming, rural non-farming, and non-rural environments was 2.3%, 5.3%, and 5.7%, respectively. After adjusting for important factors including: male sex, parental history of asthma, atopic sensitization, obesity, and parental tobacco smoking, children dwelling in a farming environment were found to have a reduced risk of asthma, compared to children dwelling in rural non-farming environments. Odds ratios (OR) were 0.22 (95% CI: 0.07 to 0.74) and 0.39 (95% CI: 0.24 to 0.65) for children with and without parental history of asthma, respectively. Children dwelling in non-rural environments, with parental history of asthma, had an increased risk of developing asthma when compared to children dwelling in rural non-farming environments (OR=2.51, 95% CI: 1.56 to 4.05). From this population-based study, dwelling in a farm environment is clearly protective for the development of asthma. This association, however, was significantly influenced by a history of parental asthma or atopy, with higher rates of incidence for asthma occurring in children with parental history of asthma and dwelling in non-rural areas, and with lower rates occurring in children with parental history of asthma and dwelling in rural farming areas. This study expands on similar findings from several observational cross-sectional studies, which previously suggested that environmental factors operating at different developmental stages appear to influence the development of asthma. Genetic factors are also important and may modify this association. By understanding the differential effects of genetic factors, and the constitution of environments that are associated with an observed lower risk of developing asthma, causal mechanisms may be elucidated and a greater insight may be available for the primary prevention strategy for asthma. Further longitudinal studies are required to evaluate the role of factors that are directly or indirectly related to the farming environment, for example: the impact of exposure to bacterial compounds in places where livestock are kept.

5.2.2 Early Life Exposures at Infancy and their Effect on Asthma

Although the study presented in Chapter 2 clearly demonstrates that some aspects of the farm environments might protect against the development of childhood asthma, whether the farming environment by itself confers the protection or whether it acts as a marker for other environmental exposures that may increase the likelihood for early infection in the environment, remains unclear. For this reason, the study discussed in Chapter 3 was conducted: 1) to examine early life predictors of asthma and wheezing incidence, and 2) to examine whether or not environmental exposures that increase the opportunity for early infection confer important protection for the development of asthma and wheezing, as proposed by the hygiene hypothesis. The study sample was comprised of infant and toddlers (less than 2 years of age) selected at baseline from the early child development cohort of the NLSCY. Outcomes were determined as the incidence of physician-diagnosed asthma and wheezing when the children were in their preschool years (2 to 5 years old). Overall, the 4-year cumulative incidences were 13.7% for asthma and 18.4% for wheeze, at the preschool age.

Impact of early wheezing

In the multivariate model, wheezing among infants and toddlers was an important independent risk factor for developing asthma at a preschool age [Hazard ratio (HR), 2.23; 95% CI: 2.03-2.65]. The role of early wheezing in the development of childhood asthma has been recently debated in numerous publications. While an association between early wheezing and risk for atopy in childhood was identified in some studies,[22-24] the evidence for asthma is not conclusive. The results from Chapter 3 indicate that infants and toddlers with persistent wheeze may need interventions to reduce the burden of developing asthma later in life. Likely, those who might gain most from early intervention are children with histories of obstructive lungs, airway hyper-responsiveness, and the presence of atopy[25]

Contribution of early exposures

The following baseline variables: breastfeeding for more than three months, upper respiratory infection, early daycare attendance, presence of older siblings at birth, and dwelling in rural areas were found to be important predictors of a lower incidence of asthma at the preschool age. Factors that predict higher incidences of both asthma and wheeze at the preschool age were: male sex, maternal use of prescription medication, single parent household, and history of parental asthma or allergy. The lower incidence of asthma associated with factors such as early respiratory infection, daycare attendance, presence of older siblings, and dwelling in rural and farming areas emphasizes the importance of early environmental exposure in the development of childhood asthma. These findings support the hygiene hypothesis that opportunities for early exposure to environmental settings with microbial derivatives could be an important factor in reducing the incidence of asthma. Nevertheless, mechanisms that lead to lower incidence of asthma and wheezing from less clean and more crowded environments are still unclear and should be further investigated. Recently, a study that investigated children living in homes regularly cleaned with bleach reported a lower occurrence of asthma and other atopic diseases including eczema.[26] This finding argues against the idea conveyed by the hygiene hypothesis that cleanliness *per se* increases the risk of asthma and allergies.

5.2.3 Risk Factors for Wheezing Phenotypes in Early Life

The study in Chapter 4 defines the phenotypes of wheezing conditions that may occur among children in the first decade of life and determines whether or not different sets of risk factors associated with these phenotypes are suggestive of a different etiology. Longitudinal data for children under the age of two years was used to examine several prenatal, perinatal, and early childhood factors that are predictors of these wheezing phenotypes. Information on current wheeze (occurring within the past 12 months) was collected prospectively at five cycles conducted every two years. This was used to define five wheezing phenotypes as: non-wheezers, preschool wheezing, primary school-age wheezing, intermittent wheezing, and persistent wheezing. The independent predictors of wheezing phenotypes included: male sex, breast-feeding, prematurity, personal allergy, low health status at birth, early respiratory infection, daycare attendance, parental asthma, crowding and poor dwelling condition that need repairs. The effects of these factors varied between the wheezing phenotypes. Parental asthma and child's allergy had a stronger association with persistent wheezing than with preschool wheezing. Daycare attendance in the first year of life was a risk factor for preschool wheezing but was a protective factor for primary school wheezing. This study identified the different sets of risk factors as predictors for each wheezing phenotype albeit with some degree of overlap. The observed differential effect for these conditions thus raises the possibility of a different etiology for the development of asthma among children.

5.3 Public Health Implications and Recommendations

Childhood asthma and wheezing illness accounts for a significant burden and health care cost in most developed countries including Canada.[27,28] In recent randomized studies conducted among Canadian children, intervention measures introduced before and during the first year of life such as avoidance of house dust, pets,

ETS, and encouragement of breastfeeding with delayed introduction of solid food was effective in reducing the incidence of asthma later in life.[29-31] In a population based cohort study, protective factors identified include breastfeeding for at least three months, daycare attendance, and dwelling in rural and farming areas. Factors associated with an increased risk of developing asthma include early wheezing, male sex, maternal smoking during pregnancy, low birth weight, low socio-economic status, parental atopy, and living in a single parent household. Although not all factors identified are amenable to public health intervention efforts, knowledge of them is important for identifying those individuals in the population who may benefit from future preventative interventions. For instance, factors such as parental history of asthma and atopic status of the individual host, which have important association with the development of asthma phenotypes, can be used to identify high-risk children for prevention efforts. Furthermore, primary prevention for modifiable risk factors such as home repairs, maternal smoking during pregnancy, and young maternal age, that have shown to be important risk factors, can be developed through education programs. In addition, a longer period of breastfeeding is protective for asthma, and should be encouraged among mothers. Thus, public health intervention strategies can be developed by health care professionals when working with new mothers to provide accurate and continuous education and information about the benefits of breast-feeding.

In summary, the results of this study provide a better understanding of the role of environmental factors – especially factors that increase the opportunity for early infection among children – that may play a role in the development of early childhood asthma and wheezing. Nevertheless, conclusions from this study should be drawn with caution. Intervention program in early childhood such as the *Canadian Childhood Asthma Primary Prevention Study*[29-31] are required to elucidate the benefit of the protective factors identified in this thesis for the development of asthma.

5.4 Limitations

The main limitation of this study is that, the study outcome – physician-diagnosed asthma and wheezing – was not confirmed by a physician or by chart review. As a result, these outcomes may be subject to some recall bias that might under- or over-estimate the true incidence in the population. Parental reports of asthma and wheezing, however, were verified in a random sub-sample of the NLSCY, by examining the agreement in responses to the use of ventolin and other inhalants on a regular basis. Also, at baseline, the parental reports on current asthma, occurring in the past 12 months, were in excellent agreement with the physician-diagnoses of asthma among children (kappa coefficient=0.92). Second, the interviewers' perception, for differentiating the dwelling areas, may be biased and may not accurately reflect the actual dwelling environments of the children. The factors considered in this thesis were those which were collected as part of the NLSCY and unmeasured factors were not considered in any of the analysis conducted in the thesis. Although sensitization to house dust might, molds and other allergen such as ownership of pets especially cats, dogs, and horses are important factors in the development of asthma, the information about these factors was not available in the NLSCY. Hence, there was no opportunity to explicitly examine these factors in any of the analyses presented in the current thesis.

Finally, no universally accepted definition exists for wheezing phenotypes among children. Hence, the results of this study cannot be directly compared to those of previous studies, with similar objectives but using different definitions.

5.5 Conclusions

In conclusion, this study used data from the largest longitudinal observational study ever conducted in Canada to identify the early-life factors that determine the development of asthma and wheezing in children. Notwithstanding the limitations mentioned above, the study identified several modifiable factors which predict the incidence of asthma and wheezing among children. Although some degree of variability existed among the risk-factors observed for wheezing phenotypes, some common factors emerged. A high rate of asthma occurred in children with persistent wheezing, which was strongly associated with either personal atopy or a familial history of asthma. These results indicate that genetic factors are important determinants of these phenotypes. A history of respiratory infection was a risk factor for wheezing phenotypes, but also protected against the development of asthma. Daycare attendance in the first year of life was a risk factor for preschool wheezing, but was a protective factor for primary school wheezing. Clearly, variant wheezing phenotypes that may occur in early childhood have different risk factors. This suggests that a different etiology may underlie these conditions, and thus, different public health interventions need to be developed for the various populations that are at risk. More research is also required, especially with regard to longer periods of follow-up, for exploring novel intervention strategies in the primary prevention of asthma and wheezing conditions among children.

5.6 Suggested Future Work using the NLSCY

The data from the ongoing Canadian National Longitudinal Survey of Children and Youth can be used in future for the following among others:

1) Examining the recurrent rate of asthma and wheeze over time.

2) Assessment of differences in recurrence of asthma attack and wheeze, by age groups.

3) Repeated cross-sectional analysis of the NLSCY to examine changes in risk factors for current asthma and wheeze at each cycle.

4) Deriving longitudinal marginal models[32-34] to obtain average effects of the predictors of asthma and wheeze across time.

5) Examination of the development of asthma at the individual and household levels – i.e., using a multilevel analysis[35-38] to partition the variance occurring at these levels.

6) Examination of the impact of contextual factors (i.e., contributing factors at parental or household levels) on the development of asthma at the individual level.

7) Assessing the potential predictors of individual growth or decline rates for recurrent attacks of asthma.

8) Assessing the geographic variability in the occurrence of asthma and wheezing among the dwelling centers of Canada.

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Appendices

Appendix A

A.1 The National Longitudinal Survey of Children and Youth Data

A.1.1 Overview

The first Canadian National Longitudinal Survey of Children and Youth (NLSCY) study was jointly conducted by Statistics Canada in 1994-1995 and the Human Resource Development of Canada (HRDC) under the federal government's "brighter initiative" for children living in Canada. At the baseline, 22,831 children (ages less than 12 years) from all ten provinces in Canada were surveyed. Table A.1 provides an overview of the first five cross-sectional samples which were conducted up to the time of the preparation of this thesis (NLSCY release 2003 and release 2005).

Trained interviewers administered each survey in-person to the person most knowledgeable" (PMK) about the child – usually the PMK was the biological mother (mother: 91.3%; father: 8.2%; non-parent: 0.5%). The PMK acted as the proxy respondent to provide all information required in the survey including the child's demographic information, and parental, household, and neighborhood factors, as well as medical condition such as current and previous physician-diagnosed asthma, current wheezing, and several respiratory symptoms that occur in prenatal, infant, and preschool years. Details of the survey were published in the micro data user's guide.[1,2]

In this appendix, only brief characteristics of the NLSCY data, as used in this thesis, are provided.

A.1.2 Sample Design of the NLSCY

The primary objective of the NLSCY is to monitor the development of Canadian children as they grow from childhood to adulthood. To accomplish this goal, a large representation of the geographic and socioeconomic make-up of Canadian children was used for the survey. Children (ages less than 12 years) were surveyed from 13,439 households in the first cycle, conducted in 1994-1995. These households were chosen from main, integrated, and the territories components, described below.

A.1.3 The NLSCY Main Component

Households included in the main component of the NLSCY were selected from the Canadian Labour Force Survey (LFS).[3] In brief, the LFS is a monthly survey designed to collect labor market data from a national sample of about 60,000 dwellings representing about 97% of the population (15 years of age and older) in Canada. The design of the LFS survey employed a two-stage sampling frame to select the study subjects. First, city blocks were randomly chosen, and households were randomly selected within these blocks. Households from the Yukon, Nunavut and Northwest Territories, and persons living on Indian Reserves, full-time members of the Canadian Armed Forces and inmates of Institutions such as chronic care hospitals, prisons, and child residential facilities were excluded from the LFS. Therefore, these populations were not captured in the main component of the NLSCY. In the LFS, demographic information for all family members, including the head of the economic family, were collected for each selected household. Approximately 12,000 households were selected for the sample that was included in the NLSCY main component.

A.1.4 The NLSCY Integrated Component

At the same time when the NLSCY was conducted, Statistics Canada again conducted a National Population Health Survey (NPHS) to estimate the prevalence of physical and mental health in Canadians, and to determine factors associated with their health problems. For households that were selected from those listed in the LFS, if a randomly selected person from a household was 11 years old or less, the household was indexed as part of the NLSCY study; otherwise, the household was considered as part of the NPHS. Approximately 2,700 households were selected for the NLSCY integrated component.

A.1.5 The NLSCY Territories Component

The NLSCY territories component was also integrated with the NPHS. Since households from the LFS sampling frame excluded the population from the Yukon and the Northern Territories, new households were sampled from the population of occupied private dwellings in those territories, as part of the NPHS. Again, each selected household, with children who were 11 years old or younger, was included in the NLSCY. One person in each household was selected at random and if that person was 11 years old or younger, the NLSCY was administered; otherwise the NPHS was administered. Persons from institutions and unrecognized areas were excluded from both the Yukon and Northwest Territories. In addition, the Northwest Territories sample excluded very remote areas and very small communities. Approximately 2,300 children were sampled from the Territories. Because of data linkage and confidentiality-related issues, the analysis performed in this thesis did not include data from the territories component.

A.1.6 Survey Methodology and Data Collection

Children were selected at random from eligible households, and the proxy respondent or the PMK completed questions about the demographics of occupants, relationship between occupants, and dwelling conditions. Up to a maximum of four children were randomly chosen from each economic family or household, listed in the NLSCY at baseline. Subjects included family members, blood relatives, relatives by marriage, common law relationships or adoptions, and foster children. At each cycle, data preparation and preliminary checks against previous information was performed by trained personnel from Statistics Canada to determine any inconsistent or invalid responses.

A.2 Description of the Study Cohort

The NLSCY study, beginning at Cycle 1, was conducted in 1994-1995 with a sample of 23,831 children surveyed cross-sectionally at the baseline (Table A.1). Of these, 16,903 children were indexed as a longitudinal cohort for a follow-up study. This sample formed Cohort 1 of the NLSCY study. The intention was to re-survey each subject in this cohort every two years until each child had attained the age of 25 years. The size of the initial cross-sectional sample was reduced, mainly because of the response burden on households with more than two children. Tables 6.2 and 6.3 present the response distribution of the baseline cohort, by each Canadian Province and age group, as they were followed through the first five cycles used in this thesis.

The longitudinal response rate at Cycle 2 was 91.5%. At Cycle 3, an attempt was made to convert non-respondents in Cycle 2 back into the survey. All initial subjects, indexed at Cycle 1 as longitudinal subjects, were re-contacted, except for deceased children, duplicate cases, children who were the wrong age for the survey, children of households that were not traceable in Cycle 2, children of households that had moved permanently out of the country, children on Indian reserves, and children of households that adamantly refused to be recorded in Cycle 2. By Cycle 3, 11.3% of the children indexed from Cycle 1 were lost to follow-up.

The NLSCY continued to interview Cycle 1 children at Cycle 4 but decided to exclude households after two consecutive cycles of non-response. Of such households, 518 were excluded in Cycle 4. In addition, hard refusals (n=473), deceased children (n=7), children who had moved permanently out of the country (n=79), and children who had not responded in Cycle 2, or had moved temporarily in Cycle 3 (n=8), were excluded. Children were also considered to be non-respondents after two consecutive cycles. In all, the longitudinal response rate at Cycle 4 was 78.7% for children in the initial cohort, which was followed from Cycle 1 (Table A.2). By Cycle 5, some children were 18 or 19 years old. When the children attained the age of 18 years old, they became the primary respondents, instead of the PMK, and made the decision to respond or not to the survey. The response for this age group at Cycle 5 was less than that for the younger children, when the PMK completed the questionnaire (Table A.3). At each cycle, attempts were made to re-contact and survey all non-respondents in previous cycles, so as to retain more cases in the longitudinal sample. Nevertheless, households that had three consecutive cycles of non-response by Cycle 5 were excluded. Also excluded from the sample in Cycle 5 were hard refusals (n=192), deceased children and youth (n=8), children and youth who had permanently moved out of Canada (n=72) and children and youth on Indian reserves (n=10). In all, by Cycle 5, the longitudinal response rate was 74.1% for children in the initial cohort from Cycle 1, of which 65.9% responded in all of the 5 cycles (Tables 6.2 and 6.3).

A.2.1 The Early Child Development Cohort

At Cycle 2 of the NLSCY conducted in 1996-19997, a new cohort of children ages less than 2 years old was introduced as the first cohort of the Early Child Development study initiated by Statistics Canada. The primary objective was to monitor the impact of early life factors on the development of health in Canadian children before a school age (<6 years). Figure 1.1 in Chapter 1 provides the design of the ECD study shown as a component of the main NLSCY, which was appended from Cycles 2 to 5.

Panel 1of the ECD study represents Cohort 2 of the NLSCY study (Table A.4). About 2,000 children (aged 0 and 1) were selected at baseline. This cohort was followed for only three cycles (Cycles 2 to 4), which were not part of the NLSCY sample at Cycle 5. Two sources were used to select the sample: first, children were selected from the LFS; and then siblings of children remaining in the NLSCY Cohort 1 sample were added. A total of 4,154 children were included in the first ECD panel. The distributions by Canadian province for the longitudinal response rate for this cohort are presented in Table A.4. When the first ECD panel arrived in Cycle 3, only responding siblings of children from the longitudinal sample in Cohort 1 were contacted. In Cycle 4, Panel 1 was of the 4 and 5 year old children. This was the last survey conducted on these children with a response rate of 68.0% (Table A.4).

The second ECD panel, or the NLSCY Cohort 3, was the new subject of children (aged 0 and 1) that had been introduced at Cycle 3 (1998-1999) (Table A.5). At this point, the ECD initiative was also interested in "the readiness to learn" aspect of children who were entering the school system. Hence, a large sample of 5 year-olds was determined to be needed for meeting the analytical goals. Simultaneously, a larger sample of 1 year old children was selected in Cycle 3 to meet those objectives, once they became the 5 year-old children in Cycle 5. A sample of about 10,000 was targeted. Also, a sample of approximately 2,000 children (aged less than 12 months) was selected using the LFS. Because of the overlap between the two frames, certain eligible children were dropped from the selection, since their households had already been selected for children in the other cohorts. The sample included 8,126 children (aged less than 2 years), after excluding the children in households already in the survey. For children introduced in Cycle 3, the response rate at NLSCY Cycle 5, where the study was terminated, was 87.5% (Table A.5).

The NLSCY Cohort 4 was introduced in Cycle 4 as the third ECD panel (2000-2001) (Table A.6). Again, the baseline sample was comprised of children (aged 0 and 1 year), selected from the LFS. For the 4,008 children introduced in Cycle 4, a total of 3,476 (86.7%) were contacted again in Cycle 5. The cohort will be surveyed for the last time at Cycle 6 (Data not available at the time of this thesis).

NLSCY Cohort 5 was initiated as the fourth panel of the ECD study (Table A.6). It comprised children (aged 0 and 1 year) who were introduced from the LFS in Cycle 5. These children will be surveyed twice at Cycle 6 and Cycle 7, when they will be 3 to 4 years, and 5 to 6 years of age. (Data not available at the time of this thesis.)

A.3 Questionnaire

In each survey, until children attained the age of 18 years, the PMK completed the general questionnaire, parent questionnaire, and the child questionnaire,[2] which included basic demographic information for each household member, dwelling conditions, and other household variables.Tables 6.7 to 6.8 list some of the NLSCY questionnaire variables used in this thesis.

A.4 Reliability and Validity of the NLSCY Variables

A.4.1 Independent Variables

The NLSCY expert advisory group determined the content area of the NLSCY variables, which covers risk factors, protective factors, and several child outcomes such as the health utility indices. Survey instruments were tested by qualitative focus groups, one-on-one interviews, and two field tests. If the scales used in the NLSCY questionnaire were modified or adapted from established scales, then the tests were conducted to ensure that reliability and validity of the scales were maintained. All measures used in the NLSCY questionnaire have been outlined in detail with references, in the overview of the survey instrument. Operational definitions for each study variable used in Chapters 2 to 4 were explicitly described in Tables 6.11 to 6.14.

A.4.2 Validation of Asthma and Wheezing Questionnaire

Parental-report of asthma and wheezing was verified by examining the agreement with response to the question: "Does he/she take any medication on a regular basis: ventolin or other inhalants?" The measure of agreement (Kappa) ranged from 0.58 to 0.71 for the cross-sectional data collected between Cycles 1 to 5. In a validation study conducted among Canadian children, parental-report on an asthma questionnaire had good agreement with the physician classification (Kappa=0.77; sensitivity=0.95; and specificity=0.85), and a free-running exercise test, at 10 min.[4]

A.5 Methods for the Longitudinal Analysis

In longitudinal studies, such as the NLSCY, a correlation may arise in the data due to repeated observations taken for the same individual at several points in time. Also, observations made on clusters of subjects selected from the same family, household, or neighborhood may be correlated. Several techniques, such as the generalized estimating equation,[5-15] multilevel modeling,[16-23] and bootstrapping methods,[24,25] have been incorporated in statistical methods including logistic and survival analyses to account for correlations in repeated longitudinal measurements or in clustered data. Where appropriate, some of these approaches have been implemented in this data analysis to account for correlations among subjects in the NLSCY data. For time-to-event data analysis, as employed in Chapter 4, a modified Cox's regression for survey data was employed.[26,27]

A.6 Sample Size

In general, the simplified formula for sample size calculation in cross-sectional studies using a univariate regression with binary outcome Y, (Y=1 (success) or 0 (failure)) and a single binary independent variable X, (X=1 or 0) has been given by Hsieh *et al.* (1998) as: [28, 29]

$$N = \frac{(z_{(1-\alpha/2)} + z_{(1-\beta)})^2 \overline{p}(1-\overline{p})}{(p_1 - p_o)^2 r(1-r)} \qquad (1)$$

where N is the required sample size, $z_{(1-\alpha/2)}$ is the (1-α/2) percentile point of the standard normal distribution, $z_{(1-\beta)}$ is the (1-β) percentile point of the standard normal distribution, $\overline{p}$ is the weighted average of p_0 and p_1, and r is the proportion of the sample with X=1, p_0 and p_1 are the prevalence rates with X=0 (reference group), and X=1 (exposed group).

For a longitudinal study where the T measurement is expected to be taken in the follow-up period, given that the outcome and independent variable are dichotomous, the equation for the sample size calculation for the cross-sectional study can be adjusted with the correlation coefficient (ρ) between the repeated measurements, as follows[30]:

$$N = \frac{(z_{(1-\alpha/2)} + z_{(1-\beta)})^2 \overline{p}(1-\overline{p})(r+1)[1+(T-1)\rho]}{(p_1 - p_o)^2 r(1-r)T} \qquad (2)$$

Based on equation 2, the sample size for the different scenarios of $(p_1 - p_o)$, that represents differences in the expected proportion between the reference and the exposure categories at the end of the study; and the correlation coefficients, are presented in Table A.10 for three and four repeated measurements.

For multiple logistic regressions, the sample size is multiplied by an inflation factor $1/(1-\gamma^2)$, where γ is the multiple correlation coefficient for factor X with other independent variables. For instance, in a study of asthma, where the binary outcome is "current asthma" and "current wheeze" and the binary predictor X_1, (X_1=1 or 0) indicates the presence or absence of exposure (obesity), when the overall prevalence of the outcome is 12% in the exposed group and the prevalence of outcome is 8% in the non-exposed group, at 80% power and a 5% level of significance with the assumption that the prevalence of the exposure is about 15% in the population, a sample size of 381 children is required for the logistic regression analysis.[31] This sample size would increase to 507 for a multiple logistic regression of the outcome, with predictor variables X_2, which have a multiple correlation coefficient of 0.5 or less, with an X_1 indicator.

To adjust for clustering of children within a household in the NLSCY study, the sample size calculation is similar to equation 2 above. The inflation factor is now $[1+(m-1)\tau]$ where m is the maximum number of subjects selected from each household and τ is the intra-cluster correlation.[32] Since m (=2) is small in the NLSCY study, and over 77% of the surveyed households had only 1 child, τ would usually be less than 0.1 and the sample size of 16,903 children, indexed at baseline as the longitudinal cohort with a retention rate of 65.7% (11,136/16,903) at Cycle 5 (for those who participated in all four surveys of the NLSCY), is adequate for the analysis presented in this thesis.

A.7 Non-Responses and Missing Data

Some of the main methodological problems in longitudinal studies are due to non-respondents and missing data, or attrition, since an unpleasant situation may be involved (i.e., the outcome of interest under investigation). In longitudinal follow-ups, if the missing data or non-responses are "not" dependent on previous observations, or on the outcome of interest, then they may be considered as "ignorable missing information" in the analysis, with no consequence to the interpretation of the result. Otherwise, if the missing data is "non-ignorable," then the study results would be subject to potential bias. In this thesis, retention analysis[30] was performed in each case to determine if factors are correlated with intermittent missing data. The results were interpreted in light of the findings from the retention analysis.

A.8 Weights for Longitudinal Analysis

Participants in the NLSCY were selected using probability sampling methods. That is, children were included in the sample as representing a certain number of populations of children dwelling in Canada. Therefore, population weights for both cross-sectional and longitudinal analysis were provided by Statistics Canada for children in the survey at each cycle. In addition to the population weights provided by Statistics Canada, each NLSCY micro data file had 1,000 replicates of bootstrap weights for each subject. Statistics Canada emphasized the use of these bootstrap weights in the analysis, to generate standard errors for statistical inference.

A.9 Access to the NLSCY Data Files

For this thesis, the Social Science and Humanity Research Council of Canada (SSHRC) granted permission to assess the confidential micro data at the Statistics Canada Research Data Centre (RDC), housed in the Rutherford Library at the University of Alberta. See Appendix C for the copy of the Statistics Canada research contract and the permission letter.

A.10 Tables

Table A.1 Data collection periods for each NLSCY cycle

NLSCY Cycles	Cross-sectional Sample	ECD cohort	Longitudinal cohort	Start to End date
Cycle 1	22,831	N/A	16,903	Dec. 1994 to April 1995
Cycle 2	20,025	4,557	15,468	Dec. 1996 to April 1997
Cycle 3	32,223	17,886	14,997	Oct. 1999 to June 1999
Cycle 4	30,307	16,997	13,310	Sept. 2000 to May 2001
Cycle 5	25,439	12,916	12,523	Sept. 2002 to June 2003

ECD=Early Child Development study

Table A.2 Unweighted longitudinal response rate for *Cohort 1* by Province

Canadian Provinces†	Cycle 1 (94/95) No.	Cycle 2 (96/97) No. (%)	Cycle 3 (98/99) No. (%)	Cycle 4 (00/01) No. (%)	Cycle 5 (02/03) No. (%)	All Cycles†† (94-03) No. (%)
N & L	950	892 (93.9)	845 (88.9)	777 (81.8)	755 (79.5)	689 (72.5)
PEI	467	443 (94.9)	434 (92.9)	392 (83.9)	364 (77.9)	330 (70.7)
Nova Scotia	1,191	1,068 (89.7)	1,085 (91.1)	988 (83.0)	903 (75.8)	811 (68.1)
New Bruns.	1,070	958 (89.5)	958 (89.5)	836 (78.1)	792 (74.0)	691 (64.6)
Quebec	3,182	2,944 (92.5)	2,844 (89.4)	2,522 (79.3)	2,361 (74.2)	2,108 (66.2)
Ontario	4,342	3,899 (89.8)	3,760 (86.6)	3,318 (76.4)	3,104 (71.5)	2,714 (62.5)
Manitoba	1,232	1,161 (94.2)	1,112 (90.3)	1,019 (82.7)	1,004 (81.5)	891 (72.3)
Saskatchewan	1,413	1,305 (92.4)	1,257 (89.0)	1,073 (75.9)	1,002 (70.9)	893 (63.2)
Alberta	1,599	1,465 (91.6)	1,420 (88.8)	1,242 (77.7)	1,162 (72.7)	1,031 (64.5)
British Columbia	1,457	1,333 (91.5)	1,282 (88.0)	1,143 (78.4)	1,076 (73.9)	978 (67.1)
All Canada	**16,903**	**15,468 (91.5)**	**14,997(88.7)**	**13,310 (78.7)**	**12,523 (74.1)**	**11,136 (65.9)**

N & L= Newfoundland & Labrador; PEI= Prince Edward Island; No. =Number of respondents; † Province of dwelling in Cycle 1. †† Subjects who responded in all five cycles from baseline. Complete information was available for about 2/3 of the longitudinal cohort index at baseline. The retention varies among Canadian Provinces. The highest rate was observed for Newfoundland and Labrador (72.5%) and lowest for Ontario (62.5).

Table A.3 Unweighted longitudinal response rate for *Cohort 1* by age groups

Age group, (yrs)	Cycle 1 (94/95) No.	Cycle 2 (96/97) No. (%)	Cycle 3 (98/99) No. (%)	Cycle 4 (00/01) No. (%)	Cycle 5 (02/03) No. (%)	All Cycles[††] (94-03) No. (%)
0 and 1	4,052	3,740 (92.3)	3,638 (89.8)	3,229 (79.7)	3,157 (77.9)	2,793 (68.9)
2 and 3	2,916	2,662 (91.3)	2,585 (88.6)	2,337 (80.1)	2,229 (76.4)	2,008 (68.9)
4 and 5	2,666	2,433 (91.3)	2,372 (89.0)	2,104 (78.9)	1,982 (74.3)	1,769 (66.4)
6 and 7	2,393	2,170 (90.7)	2,103 (87.9)	1,872 (78.2)	1,719 (71.8)	1,557 (65.1)
8 and 9	2,451	2,238 (91.3)	2,158 (88.0)	1,890 (77.1)	1,786 (72.9)	1,592 (65.0)
10 and 11	2,425	2,225 (91.8)	2,141 (88.3)	1,878 (77.4)	1,650 (68.0)	1,417 (58.4)
All	**16,903**	**15,468 (91.5)**	**14,997(88.7)**	**13,310(78.7)**	**12,523(74.1)**	**11,136(65.9)**

No. =Number of respondents. † Age groups at baseline (Cycle 1). [††] Subjects who responded in all five cycles from baseline. The highest attrition rate was observed for age group 10 to 11 (58.4) at cycle 5 where there were 18 to 19 years old. Reasons provided for the low attrition rate included self completion of the questionnaire at this time among this age group.

Table A.4 Unweighted longitudinal response rate for *Cohort 2* by Province

Canadian Provinces[†]	Cycle 2 (1996/1997) No.	Cycle 3 (1998/1999) No. (%)	Cycle 4 (2000/2001) No. (%)	All Cycles[††] (1996-2001) No. (%)
Newfoundland & Labrador	146	91 (62.3)	74 (50.7)	70 (47.9)
Prince Edward Island	110	68 (61.8)	52 (47.3)	52 (0.47)
Nova Scotia	252	165 (65.5)	122 (48.4)	125 (49.6)
New Brunswick	241	218 (90.5)	175 (72.6)	182 (75.5)
Quebec	820	778 (94.9)	629 (76.7)	630 (76.8)
Ontario	1,282	1,135 (88.5)	911 (71.1)	897 (70.0)
Manitoba	327	297 (90.8)	220 (67.3)	223 (68.2)
Saskatchewan	295	269 (91.2)	177 (60.0)	178 (60.3)
Alberta	353	330 (93.5)	240 (68.0)	223 (63.2)
British Columbia	328	289 (88.1)	226 (68.9)	239 (72.9)
All Canada	**4,154**	**3640 (87.6)**	**2826 (68.0)**	**2819 (67.9)**

Table A.5: Unweighted longitudinal response rate for *Cohort 3* by Province

Canadian Provinces[†]	Cycle 3 (1998/1999) No.	Cycle 4 (2000/2001) No. (%)	Cycle 5 (2002/2003) No. (%)	All Cycles[††] (1998-2003) No. (%)
Newfoundland & Labrador	568	516 (98.8)	483 (90.8)	499 (87.9)
Prince Edward Island	273	240 (87.9)	226 (87.9)	228 (83.5)
Nova Scotia	602	539 (89.5)	497 (89.5)	490 (81.4)
New Brunswick	601	525 (87.4)	473 (87.4)	482 (80.2)
Quebec	1,361	1,209 (88.8)	1,069 (88.8)	1,070 (78.6)
Ontario	1,985	1,712 (86.2)	1,473 (86.2)	1,440 (72.5)
Manitoba	656	556 (84.8)	492 (84.8)	508 (77.4)
Saskatchewan	627	536 (85.5)	473 (85.5)	487 (77.7)
Alberta	771	687 (89.1)	637 (89.1)	598 (77.6)
British Columbia	682	591 (86.7)	517 (86.7)	537 (78.7)
All Canada	**8,126**	**7,111 (87.5)**	**6,340 (87.5)**	**6,339 (78.0)**

Table A.6 Unweighted longitudinal rates for *Cohort 4* and *Cohort 5* by Province

	Cohort 4		**Cohort 5**
Canadian Provinces[†]	Cycle 4 (2000/2001) No.	Cycle 5 (2002/2003) No. (%)	Cycle 5 (2002/2003) No
Newfoundland & Labrador	124	105 (84.7)	96
Prince Edward Island	107	97 (90.7)	95
Nova Scotia	236	209 (88.6)	181
New Brunswick	206	172 (83.5)	149
Quebec	708	615 (86.9)	554
Ontario	1,268	1,081 (85.3)	987
Manitoba	305	263 (86.2)	274
Saskatchewan	330	294 (89.1)	241
Alberta	347	321 (92.1)	342
British Columbia	377	319 (84.6)	333
All Canada	**4,008**	**3,476 (86.7)**	**3,252**

Table A.7 Sample size required at 5% level with a power of 80% for studies with different correlation correction coefficient (ρ) and no. of time measurements

No. of measurements	Expected differences in proportion		
	$(p_1 - p_o)=0.1$	$(p_1 - p_o)=0.2$	$(p_1 - p_o)=0.3$
Three times			
ρ=0	194	47	20
ρ=0.25	243	59	25
ρ=0.5	291	71	30
Four times			
ρ=0	130	31	13
ρ=0.25	194	47	20
ρ=0.5	259	59	26

This table is adapted from Twisk JWR, 2003(page 282)[30] with some modifications.

Table A.8 Outcomes questionnaire data: The following questions are about asthma symptoms or related outcomes in the NLSCY

Outcomes	Questionnaire/Description of variable	NLSCY† variable name
Ever-asthma (physician diagnosed)	Q. Has he/she ever had asthma that was diagnosed by a health professional? {R: 1=Yes; 2=No}	ahlcq43a
Asthma severity	Q. Does this condition or health problem prevent or limit his/her participation in school, at play or any other activity normal for a child his/her age? {R: 1=Yes; 2=No}	ahlcq43b
Current asthma	Q. Has he/she had an attack of asthma in the last 12 months? {R: 1=Yes; 2=No}	ahlcq43c
Current-wheeze	Q. Has he/she had wheezing or whistling in the chest at any time in the last 12 months? {R: 1=Yes; 2=No}	ahlcq44
Ventolin medication usage	Q. Does he/she take any of the following prescribed medication on a regular basis: Ventolin or other Inhalants? {R: 1=Yes; 2=No}	ahlcq51a

†Note: Index of NLSCY variable names start with "a" in Cycle 1, "b" in Cycle 2, "c" in Cycle 3, "d" in Cycle 4, and "f" in Cycle 5. Eg., the equivalent of Cycle 1 variable name "ahlcq43a" in Cycle 5 is "fhlcq43a".

Table A.9 NLSCY questionnaire for selected baseline factors analyzed in Chapter 2

Factors	**Table A.9:** Questionnaire/Description of variable	variable name
Age, yr	Q. Age of the child:0-11 years at baseline{R: *1=infants/ toddlers (0-1 years); 2=pre-schoolers (2 to 5 years); school-age (6 and above)*}	ammcq01
Sex	Q. Gender of child? {1=Male; 2=Female}	ammcq02
Child allergies	Q. Does the child have any of the following long-term conditions that have been diagnosed by a health professional: ALLERGIES? {R: 1=Yes; 2=No}	ahlcq45a
Child's health status	Q. In general, would you say his/her health is:: (*5=poor; 4=Fair and 3=Good) rated low; (2=Very good; 1=excellent) rated high*	ahlcq01
No. of pediatrician visits	Q. In the past year, how many times have you seen or talked on the telephone about Child-s physical or mental health with: a pediatrician? (Enter 0 if none.) :continuous variable – range is b/w 0 to 60 : *0=None; 1=One to four; 2=five or more*	ahlcq48b
No. of physician visits	Q. In the past year, how many times have you seen or talked on the telephone about your child-s physical or mental health with: a general practitioner, family physician? (Enter 0 if none); continues variable – **range is b/w 0 to 52:** *0=None; 1=One to four; 2=five or more*	ahlcq48a
Mother's age	Q. Age of biological mother at birth of child: continuous-range is b/w 14 to 54 – *1=less than 20 years; 2=greater or equal to 20 years*	admcd18
Older sibling	Q. Number of older siblings (of the child) living in household (including full, half, step, adopted and foster siblings). This includes siblings of all ages. (Based on date of birth) (continuous variable) – **range is b/w 0 to 11:** *1=none; 2 =1 or more*	admcd09
Parental history of asthma	Q. Do(es) you/he/she have any of the following long-term conditions that have been diagnosed by a health professional: ASTHMA? : *1=Yes; 2=No*	"achpq1c" (pmk) / or "achsq1c" (spouse)
Immigrant mother	Q. Number of years since first immigrating to Canada?; – ***Derived as*** *If "null response" then mother is not an immigrant, else mothers is an immigrant.*	"asdpd02" if mother is pmk & "asdsd02" if mother is spouse

Factors	**Table A.9:** Questionnaire/Description of variable	variable name
Either parent smoked	Q. At the present time %do/does% %you/he/she% smoke cigarettes daily (=1), occasionally (=2) or not at all (=3)? – *1=Yes (1,2); 2=No (3)*	ahlpq02 & ahlsq02
Home needing repairs	Q. Is this dwelling in need of any repairs? – *1=Yes (Minor repair: including missing or loose floor tiles, bricks or shingles, defective steps, railing or siding, etc, or Major repairs : including defective plumbing or electrical wiring, structural repairs to walls, floors or ceilings, etc.)* *2=No (No repairs needed)*	ahhhq02b
Geographic region	Q. Province of residence? – *Atlantic= (Newfoundland, P.E.I, Nova Scotia, New Brunswick); Quebec; Ontario; Prairies= (Manitoba, Alberta, Saskatchewan); West Coast= British Columbia*	agehd03
Dwelling environment	Q. Based on street level frontage, how would you characterize land use on this block/road? – *1=rural farming (primarily rural, farm); 2=rural non-farming (primarily rural, residential), 3= non-rural (primarily residential and commercial, industrial, warehouse, manufacturing and others)*	aobhq07
Body mass index,	Q. What is child's height in meters (m) and centimetres (cm)? (AND) Q. What is your child-s weight: in kilograms (kg) and grams (g)? ***BMI derived as (kg/m^2).***	ahlcq03b AND ahlcq04a
Socio-economic status	Q. Socio-economic status – *This derived variable is based on the education and occupation of the PMK and spouse and household income.. See section 8.5 of the NLSCY User-s Handbook and Microdata File Guide for further details*	ainhd08
Crowding index	Q. How many bedrooms are there in this dwelling? (If no separate, enclosed bedroom enter "00".) (Bed rooms range=0 to 12) (AND) Q. Total number of persons in the household (including the child) (Total persons: range =2 to 15) ***Index derived as*** the number of people in the home divided by the number of bedrooms in the home	ahhhq03 AND admhd02

Table A.10 NLSCY questionnaire for selected baseline factors analyzed in Chapter 3

Factors	**Table A.10:** Questionnaire/Description of variable	variable name
Male sex	Q. Gender of child? – *1= Male; 2= Female*	bmmcq02
Geographic regions	Q. Province of residence? – *Atlantic= (Newfoundland, P.E.I, Nova Scotia, New Brunswick); Quebec; Ontario; Prairies= (Manitoba, Alberta, Saskatchewan); West Coast= British Columbia*	bgehd03
Maternal age, yrs	Q. Age of biological mother at birth of child – continuous: range b/w 13 to 46: *1=<20, yrs; 2=20-25, yrs; 3=26-30, yrs; 0=>30 yrs*	bdmcd18
Prenatal problems	Q. Number of prenatal problems experienced (Includes diabetes, high blood pressure and other physical problems. Other physical problem counts as one problem.) ***Derived as*** if "0" no problem, else prenatal problems	bmdcd01
Cesarean delivery	Q. Was delivery virginal or Caesarian? – *1= Virginal ; 2=Caesarian*	bmdcq16
Low Birth weight	Q. Birth Weight, grams? – *2 = Low (<=2500 g); 1= Normal >2500g*	bmdcd08
Ever breastfed	Q. For how long did you breastfed? 0=*None; 1=Less than 3 months; 2=3-6 months; 3=> than 6 months.*	bmdcq27
Number of older siblings at birth	Q. Number of older siblings (of the child) living in household (including full, half, step, adopted and foster siblings). This includes siblings of all ages. (Based on date of birth) (continuous variable)	bdmcd09
Childhood allergy	Q. Does the child have any of the following long-term conditions that have been diagnosed by a health professional: ALLERGIES? – *1=Yes; 2= No*	bhlcq45a
Ever had nose or throat infection	Q. How often does the child have nose or throat infections? *– 1=frequently; 2= Often ; 3=Sometimes ; 4=Rarely ; 5= Never*	bhlcq46
Ever attend daycare	Q. Do you currently use child care such as daycare or babysitting while you (and your spouse/partner) are at work or studying? – *1=Yes; 2=No*	bcrcq1a
Either parent smoke	Q. At the present time %do/does% %you/he/she% smoke cigarettes daily (1), occasionally (2) or not at all (3)?	bhlpq02 & bhlsq02

Factors	**Table A.10:** Questionnaire/Description of variable	variable name
Maternal smoking	Q. How many cigarettes per day did you smoke during your pregnancy with this child? (Continuous) ***Variable derived** as "0" if none; otherwise mother smoke in pregnancy*	bmdcq04
Maternal use of prescription medication	Q. Did you use prescription medication during pregnancy? *– 1=Yes; 2=No*	bmdcq09a
Single parent household	Q. Child's single parent status (includes biological, adoptive, step, and foster parents) – Child lives with *0=None; 1= one parent; 2= Two parents*	bdmcd04
Parental atopy	Q. Do (es) you/he/she have any of the following long-term conditions that have been diagnosed by a health professional: ASTHMA? : *1=Yes; 2=No*	"bchpq1c" if PMK & "bchsq1c" if Spouse
	Q. Do(es) you/he/she have any of the following long-term conditions that have been diagnosed by a health professional: OTHER ALLERGIES? – *1= Yes; 2=No* ***Variable derived as "YES" response for either of the conditions***	"bchpq1b" if PMK & "bchsq1b" if spouse
Household socio-economic status	Q. Socio-economic status – This derived variable is based on the education and occupation of the PMK and spouse and household income. – range is b/w -3.511 to 3.031	binhd08
Crowding	Q. How many bedrooms are there in this dwelling? (If no separate, enclosed bedroom enter "00".) – Bedrooms range b/w 0 to 12 (AND)	bhhhq03 &
	Q. Total number of persons in the household (including the child) – Total persons: range =2 to 15 ***Derived as the number of people in the home divided by the number of bedrooms in the home (person/bedrooms<1.5)***	bdmhd02
Rural non CMA centers	Q. CMA-Urban Centre Code ~CMAs – 1=All CMA/Urban Centers;2= Non CMA/non Urban centres	bgehd02

Table A.11 NLSCY questionnaire for selected baseline factors analyzed in Chapter 4

Factors	**Table A.11:** Questionnaire/Description of variable	Variable name
Respiratory infection	Q. How often does the child have nose or throat infections? – *1=(frequently; Often ;Sometimes ;Rarely) ; 2= Never*	ahlcq46
History of prenatal complications	Q. Number of prenatal problems experienced (Includes diabetes, high blood pressure and other physical problems. Other physical problem counts as one problem.) ***Variable derived as*** "0" if no problem, else prenatal problems	amdcd01
Sex , Male	Q. Gender of child?: - *1= Male; 2= Female*	ammcq02
Low Birth Weight	Q. Birth Weight, grams? – R. *Low <=2500 g; 1= Normal >2500g*	amdcd08
Breast-feeding	Q. Did you, his or her mother breast-feed him or her even if only for a short time? – *1= Yes; 2= No*	amdcq26
Prematurity	Pre-maturity (pre-term birth) – *1=Premature <=258 days; 2=Normal >258 days*	amdcd07
Overweight kg/m^2	Q. What is child's height in meters (m) and centimetres (cm)? (AND) Q. What is your child-s weight: in kilograms (kg) and grams (g)? ***Variable derived as BMI (kg/m^2)* > 85 percentile**	ahlcq03b (AND) ahlcq04a
Personal history of allergy	Q. Does the child have any of the following long-term conditions that have been diagnosed by a health professional: ALLERGIES? *1=Yes; 2= No*	ahlcq45a
Health status rated low at birth	Q. Compared to other babies in general, would you say that the child's health at birth was: *5=poor; 4=Fair; 3=Good; 2=Very good; 1=excellent*	amdcq22
Maternal smoking in pregnancy	Q. How many cigarettes per day did you smoke during your pregnancy with this child? – Continuous- range is b/w 1 to 50 ***Variable derived*** as "0" if none; otherwise mother smoke in pregnancy	amdcq04

Factors	**Table A.11:** Questionnaire/Description of variable	Variable name
Daycare attendance	Q. Do you currently use child care such as daycare or babysitting while you (and your spouse/partner) are at work or studying? *1=Yes; 2=No*	acrcq1a
Maternal age at birth	Q. Age of biological mother at birth of child: - range is b/w 14 to 54 : *1=<25, o=otherwise*	admcd18
History of parental asthma	Does you/he/she have any of the following long-term conditions that have been diagnosed by a health professional: ASTHMA? – *1=Yes; 2=No*	Either "achpq1c" is YES or "achsq1c" is YES
History of parental smoking	Q. At the present time do /does you/ he /she smoke cigarettes daily (=1), occasionally (=2) or not at all (=3)? – *1=Yes (if 1 or 2); 2=No(if 3)*	ahlpq02 & ahlsq02
Household SES	Q. Socio-economic status – *This derived variable is based on the education and occupation of the PMK and spouse and household income.. See section 8.5 of the NLSCY User-s Handbook and Microdata File Guide for further details* Quartiles were used in the analysis	ainhd08
Crowding	Q. How many bedrooms are there in this dwelling? (If no separate, enclosed bedroom enter "00".) (Bed rooms range=0 to 12) (AND) Q. Total number of persons in the household (including the child) (Total persons: range =2 to 15) ***Index derived** as the number of people in the home divided by the number of bedrooms in the home (n>=1.5/bedroom)*	ahhhq03 AND admhd02
Dwelling need repairs	Q. Is this dwelling in need of any repairs? – *1=Yes (Minor repair: including missing or loose floor tiles, bricks or shingles, defective steps, railing or siding, etc, or Major repairs : including defective plumbing or electrical wiring, structural repairs to walls, floors or ceilings, etc.)* *2=No (No repairs needed)*	ahhhq02b
Residing in CMA/urban centers	Q. CMA-Urban Centre Code ~CMAs – 1=All CMA/Urban Centers;2= Non CMA/non Urban centres	agehd02

Factors	**Table A.11:** Questionnaire/Description of variable	Variable name
Geographic regions	Q. Province of residence? – *Atlantic= (Newfoundland, P.E.I, Nova Scotia, New Brunswick); Quebec; Ontario; Prairies= (Manitoba, Alberta, Saskatchewan); West Coast= British Columbia*	agehd03

A.11 References

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Appendix B

Tables for Prevalence of Asthma and Related Outcomes in the NLSCY –1994 to 2003

Table B.1 Cross-sectional prevalence (%) of '*physician-diagnosed* asthma ever' by Provinces, Canadian children of ages less than 12 years, excluding the territories

Canadian Provinces[†]	Cycle 1 (1994/95)	Cycle2 (1996/97)	Cycle3 (1998/99)	Cycle 4 (2000/01)	Cycle 5 (2002/03)
Newfoundland & Labrador	12.2	16.5	17.8	21.5	23.6
Prince Edward Island	18.5	20.2	20.7	19.7	21.6
Nova Scotia	13.8	21.0	21.4	21.7	22.6
New Brunswick	12.3	14.7	17.0	18.5	20.3
Quebec	10.7	11.8	14.2	16.5	18.2
Ontario	11.1	14.3	14.5	16.8	19.6
Manitoba	9.4	13.5	15.4	16.1	17.4
Saskatchewan	8.9	11.0	12.3	14.8	16.7
Alberta	8.6	11.3	13.3	14.6	14.2
British Columbia	8.0	10.9	13.1	14.8	16.8
All Canada	**10.8**	**13.7**	**15.1**	**16.9**	**18.7**

Table B.2 Cross-sectional prevalence (%) of 'current asthma in the past 12 month' by Provinces, Canadian children of ages less than 12 years, excluding the territories

Canadian Provinces[†]	Cycle 1 (1994/95)	Cycle2 (1996/97)	Cycle3 (1998/99)	Cycle 4 (2000/01)	Cycle 5 (2002/03)
Newfoundland & Labrador	6.8	10.1	8.8	7.0	3.6
Prince Edward Island	9.2	7.4	8.1	5.9	4.3
Nova Scotia	7.3	9.4	8.7	6.5	6.6
New Brunswick	5.9	6.3	6.9	5.7	4.3
Quebec	5.1	4.6	5.8	4.5	2.7
Ontario	5.7	6.5	5.6	4.9	4.4
Manitoba	5.0	6.1	5.2	5.3	4.0
Saskatchewan	4.1	4.8	4.9	4.4	3.7
Alberta	4.4	5.0	5.3	4.3	3.7
British Columbia	4.2	4.7	5.6	4.7	4.0
All Canada	**5.4**	**6.1**	**6.1**	**5.0**	**4.0**

Table B.3 Cross-sectional prevalence (%) of 'current-wheeze in the past 12 months' by Provinces, Canadian children of ages less than 12 years, excluding the territories

Canadian Provinces†	Cycle 1 (1994/95)	Cycle2 (1996/97)	Cycle3 (1998/99)	Cycle 4 (2000/01)	Cycle 5 (2002/03)
Newfoundland & Labrador	19.7	21.3	15.8	14.5	11.1
Prince Edward Island	24.3	24.1	19.9	12.9	9.8
Nova Scotia	24.5	23.6	22.0	16.5	13.5
New Brunswick	19.7	15.7	17.2	17.0	12.8
Quebec	19.3	16.3	17.8	13.7	10.7
Ontario	18.6	17.5	16.8	13.8	11.7
Manitoba	18.8	19.8	17.6	12.0	11.3
Saskatchewan	15.2	13.6	11.9	11.7	9.6
Alberta	14.9	15.2	15.1	12.5	10.2
British Columbia	14.7	16.6	15.2	12.4	9.3
All Canada	**18.5**	**17.5**	**16.8**	**13.6**	**11.1**

Figure B.1 Percent (%) of asthma outcomes that occurred among Canadian children at each cycle of NLSCY survey: Overall sample and specific age group at baseline

Figure 6.1-A: Distribution for overall sample (0 to 11 years at baseline)

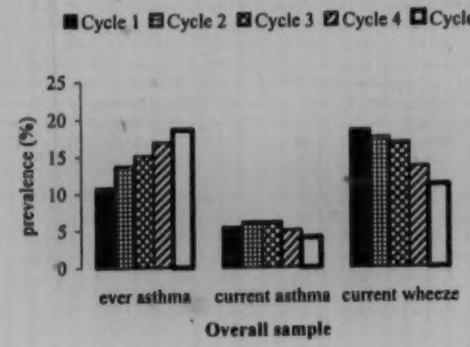


Fig. 6.1-B: Distribution for Infants and Toddlers (<2 yrs.)

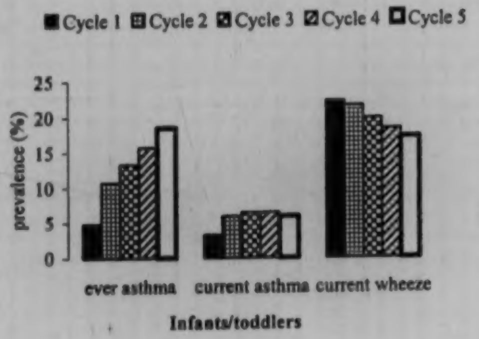


Figure 6.1-C: Distribution for preschoolers (2-6 yrs)

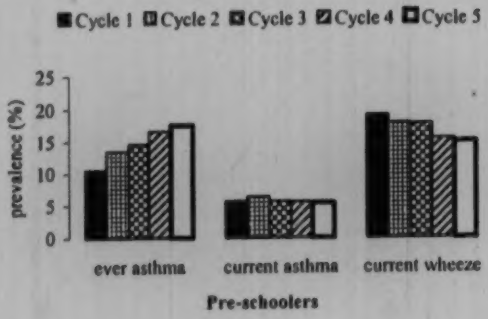


Figure 6.1-D Distribution for school -age (>6 years)

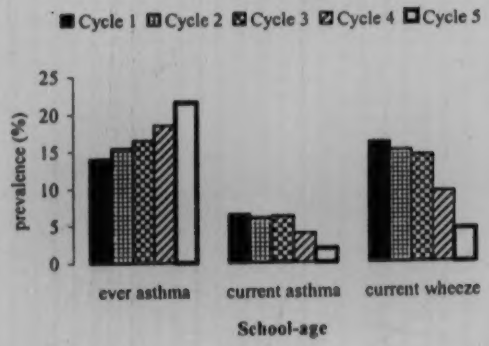
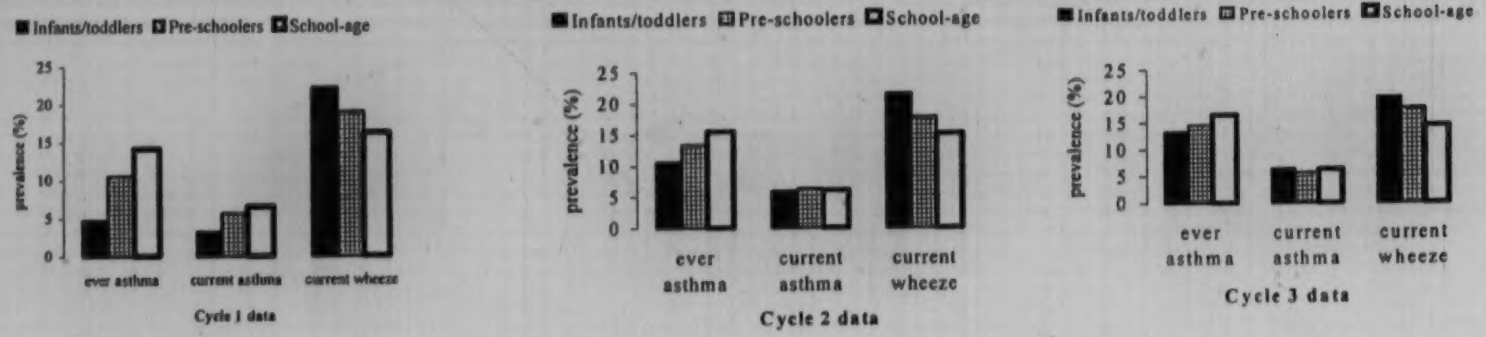


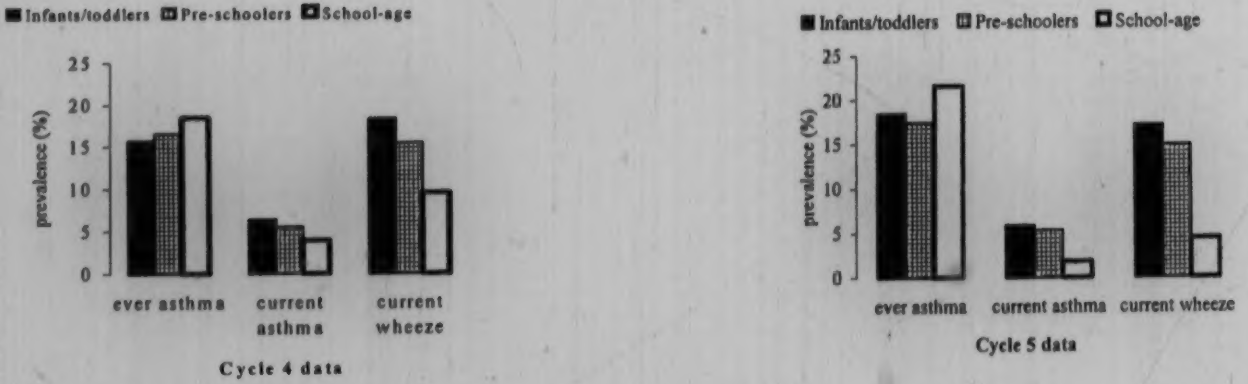
Figure B.2 Cross-sectional prevalence of ever-asthma, current-asthma and current-wheeze by specific age groups



Cycle 1 data

Cycle 2 data

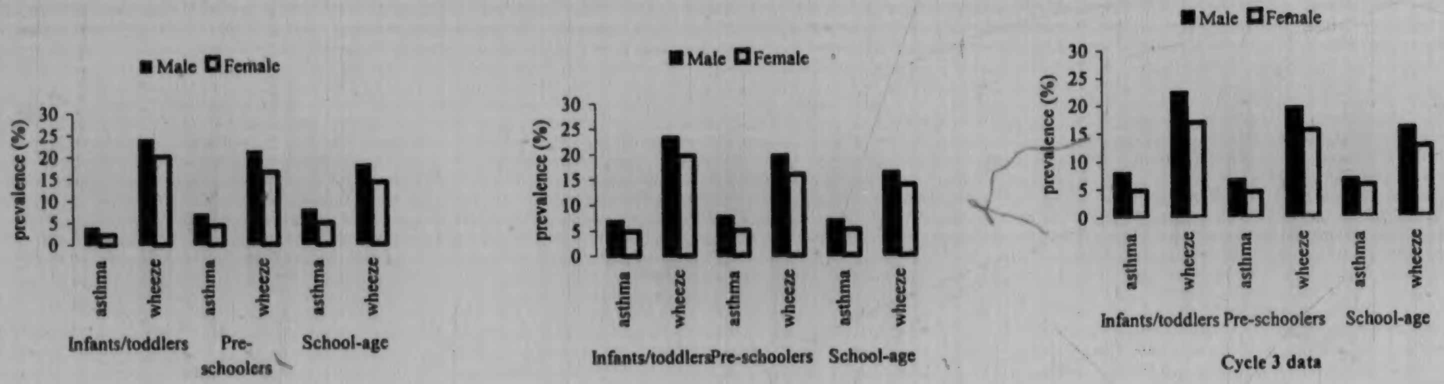
Cycle 3 data



Cycle 4 data

Cycle 5 data

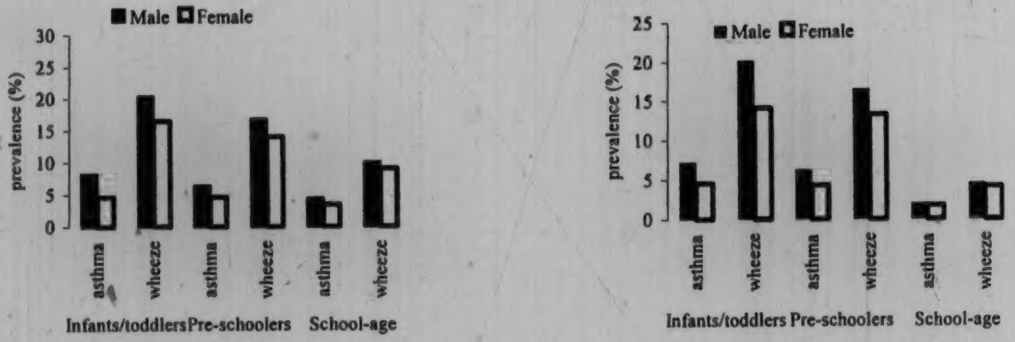
Figure B.3 Cross-sectional prevalence of current-asthma and current-wheeze by sex and age-specific groups



Cycle 1 data

Cycle 2 data

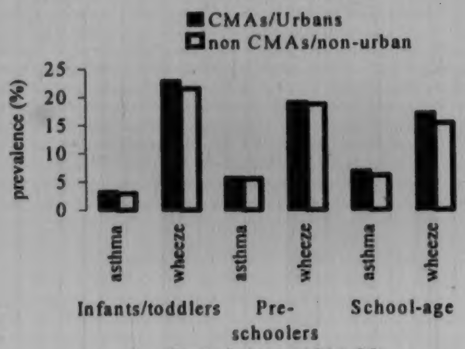
Cycle 3 data



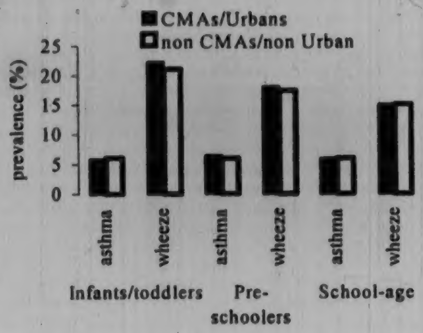
Cycle 4 data

Cycle 5 data

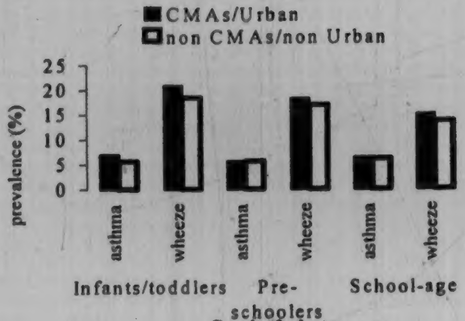
Figure B.4 Cross-sectional Prevalence of Current-Asthma and Current-Wheeze by CMA Urban and Non-Urban Centers in Canada and Age-specific Groups



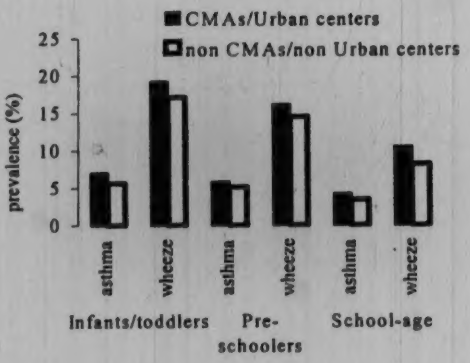
Cycle 1 data (1994-95)



Cycle 2 data

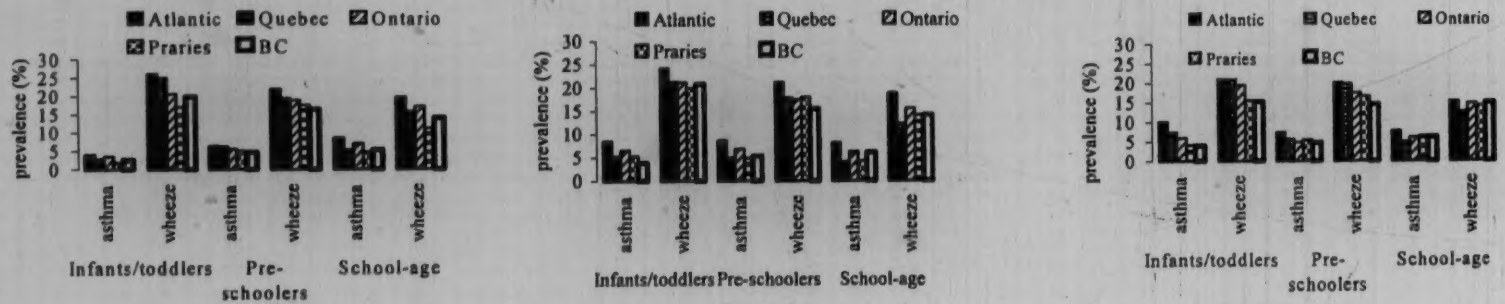


Cycle 3 data



Cycle 4 data

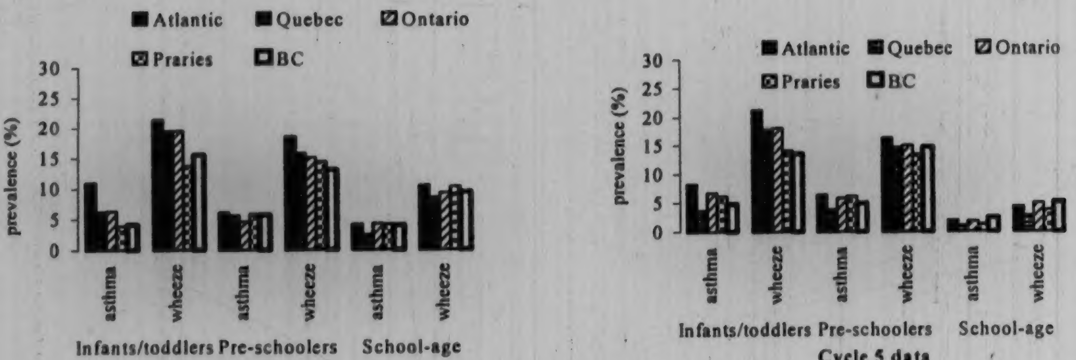
Figure B.5 Cross-sectional Prevalence of Current-Asthma and Current-Wheeze by Geographic Regions of Canada and Age-specific Groups



Cycle 1 data

Cycle 2 data

Cycle 3 data



Cycle 4 data

Cycle 5 data

Appendix C

Dissertation supporting documents

C.1 Ethics Approval for the Study

C.2 SSHRC Permission to Access NLSCY Data

C.3 Research Contract from Statistics Canada

03-SSH-UAB-0441

MICRODATA RESEARCH CONTRACT

BETWEEN:

HER MAJESTY THE QUEEN IN RIGHT OF CANADA, represented by the Minister of Industry, designated as the Minister for purposes of the Statistics Act, (hereinafter referred to as "Statistics Canada"),

AND:

Mr. William Kai Midodzi
Department of Public Health Sciences
University of Alberta
(hereinafter referred to as the "Principal Investigator"),

and,

Dr. Ambikaipakan Senthilselvan
Department of Public Health Sciences
University of Alberta
(hereinafter referred to as the "Co-investigators"),

WHEREAS Statistics Canada requires the services of the Principal Investigator to undertake statistical research and analysis on *National Longitudinal Survey of Children and Youth, Cycle 1 to cycle 4*, to fulfill its mandate under the *Statistics Act*;

AND WHEREAS to perform these services and to have access to confidential information, the Principal Investigator and the Co-investigators must become "Deemed Employees" of Statistics Canada and are required to take the Oath of Secrecy;

AND WHEREAS Statistics Canada wishes to make clear the terms and conditions under which access to the microdata will be granted;

NOW THEREFORE the Parties agree as follows:

SERVICE PROVIDED BY PRINCIPAL INVESTIGATOR

1. (1) The Principal Investigator will carry out the research project set out in Appendix "A" and provide the report described under "Proposed Output".

(2) It is understood that this is a contract for the performance of a service and the Principal Investigator and Co-investigators are engaged for the sole purpose of providing that service.

CONDITIONS OF ACCESS TO THE MICRODATA

2. The Principal Investigator and the Co-investigators must undergo an enhanced reliability check satisfactory to Statistics Canada and take the oath of secrecy in order to obtain access to the non identifiable microdata file required to perform the analysis pursuant to this contract.

3. (1) Access to the non identifiable microdata file (no names, addresses or identifying numbers) and associated documentation shall be provided on Statistics Canada premises, which includes Headquarters and the Statistics Canada Regional Offices during normal hours of operation, Monday to Friday, and the Research Data Centres,

(2) The Principal Investigator and Co-Investigators will be provided with the necessary computing facilities, software and documentation as is reasonably necessary to complete the research and analysis pursuant to this contract.

DEPARTMENTAL REPRESENTATIVE

4. The Manager of the Research Data Centre Program is the designated Statistics Canada representative responsible for the administration of this contract.

LIMITATIONS ON USES OF THE MICRODATA FILE AND PROPOSED OUTPUT

5. (1) The Principal Investigator and the Co-investigators shall not use or disclose any of the information obtained or produced pursuant to this contract for any administrative or regulatory purposes.

(2) Access to the microdata file is being provided for the statistical and research purpose outlined in the proposal attached as Appendix 'A' and the microdata file shall not be used for any other purposes without the prior written consent of Statistics Canada.

(3) The Principal Investigator and the Co-investigators shall not disclose any of the information from the individual records obtained or produced pursuant to this contract to anyone other than current Statistics Canada employees.

(4) The Principal Investigator and the Co-investigators shall ensure that no attempts are made to link the microdata file to any other files in order to relate the particulars to any identifiable individual person, business or organization.

(5) The "Proposed Output" must meet the requirements of both peer and institutional review prior to being released by Statistics Canada, for example, in one of its publications or in a research paper.

(6) Thereafter, the Principal Investigator may, subject to subsection 6(5), carry out a secondary analysis, but such analysis shall be based solely on the approved "Proposed Output" produced pursuant to this contract and be related to the analytical work undertaken to produce the "Proposed Output".

(7) The Principal Investigator agrees to work with Statistics Canada in trying to meet the requirements of peer and institutional review required for the publication or research paper. For the Research Data Centres, a timetable for conducting the peer and institutional review is available in the guidelines for producing the "Proposed Output".

(8) In the event the "Proposed Output" fails a peer or institutional review and Statistics Canada decides not to publish it, Statistics Canada will give the Principal Investigator written notice to this effect within thirty days of having made the final decision.

(9) Subject to subsections 6(5) and 10(2), in the event Statistics Canada notifies the Principal Investigator in writing that the proposed output will not be published, the Principal Investigator will not be prevented from:

(a) Publishing the "Proposed Output" elsewhere, and/or

(b) Using the "Proposed Output" for purposes of the attainment of an educational degree.

OWNERSHIP

6. (1) The microdata file and related documentation shall at all times be and remain the sole and exclusive property of Statistics Canada, it being mutually agreed that this contract pertains to the use of the microdata file and related documentation to produce a "Proposed Output" for Statistics Canada and that nothing contained herein shall be deemed to convey any title or ownership interest in the microdata file or the related documentation to the Principal Investigator or the Co-investigators. The computer equipment provided for use by the Principal Investigator and the Co-investigators must never be removed from the premises of Statistics Canada and remains the sole and exclusive property of the access facility.

(2) Statistics Canada reserves the right to publish in whole or in part, to publish an amended version or not to publish at all, as Statistics Canada deems appropriate, the "Proposed Output" produced by the Principal Investigator pursuant to this contract.

(3) Copyright in the "Proposed Output" produced by the Principal Investigator pursuant to this contract shall vest in Her Majesty the Queen in Right of Canada. The Principal Investigator shall provide to Statistics Canada at the completion of the contract or at such other time as Statistics Canada may require, a written permanent waiver of Moral rights from every author who contributed to the aforementioned material. Statistics Canada (Her Majesty the Queen in Right of Canada) hereby grants to the Principal Investigator a non-exclusive license to use, reproduce, publish and distribute the "Proposed Output" for any purpose, including, without limitation, research, teaching and publication in any medium.

(1) Secondary releases of the "Proposed Output" may be considered by Statistics Canada subject to obtaining consent from the Principal Investigator.

(5) In publishing the "Proposed Output" elsewhere, using the "Proposed Output" in the attainment of an educational degree or carrying out any secondary analysis, any reports, documents, or materials which are subsequently prepared by the Principal Investigator which use, incorporate or are in any way based on any material produced under this agreement, shall prominently display the following notice:

"The research and analysis are based on data from Statistics Canada and the opinions expressed do not represent the views of Statistics Canada."

CONFLICT OF INTEREST

7. (1) All persons engaged in the course of carrying out this contract shall conduct themselves in accordance with the principles and spirit of the *Conflict of Interest and Post-Employment Code for the Public Service.*

Should a conflict exist prior to the commencement of this contract or be acquired or develop during the life of this contract, the person with the conflict engaged in carrying out this contract shall be responsible for discussing the conflict with the Director of the Division sponsoring the project or the Manager of the Research Data Centre Project and, should it be determined that a conflict exists, for completing the Confidential Report as required by the *Conflict of Interest and Post-Employment Code for the Public Service.*

No person engaged in the course of carrying out this contract may use any of the information gained by accessing the confidential data for any other purpose except that which was agreed upon in this contract.

Notwithstanding subsection 7(3), it is understood that the principles of the *Conflict of Interest and Post-Employment Code for the Public Service* were not meant to prohibit the persons engaged in this contract from accomplishing any secondary analysis as permitted by the contract.

SECURITY REQUIREMENTS

8. (1) Any material to be removed from the Statistics Canada premises by the Principal Investigator or Co-investigators must first be screened by Statistics Canada to ensure that there is no risk of disclosure of confidential information or information that may lead to the identification of an individual respondent. It is the responsibility of the Principal Investigator or Co-investigators to take all precautions to avoid disclosure of confidential information or information that may lead to the identification of an individual respondent. The Principal Investigator or Co-investigators may remove summary files, tabulations and analytical output under the terms of this subsection.

(2) The Principal Investigator and the Co-investigators shall not remove any of the original data set or copies of subsets of the microdata file or any confidential sensitive statistical information provided pursuant to this contract from the premises of Statistics Canada.

(3) The Principal Investigator and the Co-investigators shall be provided with copies of all relevant Statistics Canada policies related to confidentiality, privacy and security and the standard operating procedures of the appropriate access facility and shall acknowledge in writing their compliance with all of the policies and operating procedures.

TERM

9. This contract comes into force when signed by both parties and shall continue in force until *March 1, 2006*, unless revoked or terminated at an earlier date.

TERMINATION

10. (1) Where the Principal Investigator is in default in carrying out any of its obligations under this Contract, Statistics Canada may, upon giving written notice to the Principal Investigator, terminate the Contract immediately.

(2) The Contract may, by providing 30 days written notice, be terminated by mutual written consent between the Principal Investigator and Statistics Canada.

(3) Any notice to be given to Statistics Canada or the Principal Investigator shall be sent by registered mail to:

Gustave Goldmann
Research Data Centres Program
SC1710 Main Building
Statistics Canada
Ottawa (ON)
Canada K1A 0T6

William Kai Midodzi
Department of Public Health sciences
13-103 Clinical Sciences Building
University of Alberta
Edmonton (AB)
Canada T6G 2G3

(4) Any notice shall be deemed to be effective on the day it is received at the address set out above.

PENALTIES

11. (1) As a Deemed Employee of Statistics Canada, the Principal Investigator and the Co-investigators are subject to all the applicable penalties provided for in the *Statistics Act* for contravention of any of the confidentiality provisions and is liable on summary conviction to any of the applicable fines or imprisonment terms.

(2) Subsection 11(1) survives indefinitely the completion of this contract or the termination of this Agreement pursuant to subsections 10(1) or 10(2).

AMENDMENT

12. No amendment to this contract shall be valid unless it is reduced to writing and signed by the Parties hereto.